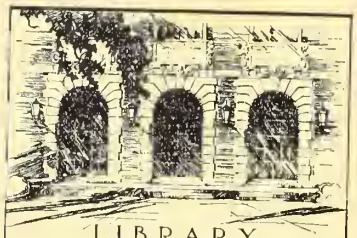

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TRANSANNULAR HYDROGEN TRANSFER REACTIONS

Reported by David Curtin September 25, 1953

Introduction.--- In an investigation of the alkylation of paraffins, Bartlett, Condon and Schneider[1] found that i-pentane reacts with t-butyl chloride in the presence of aluminum chloride in a time as short as one thousandth of a second at room temperature to give t-amyl bromide in 50-70% yield. The fundamental step in this reaction is the transfer of a hydrogen and electron pair from an i-pentane molecule to a t-butylcarbonium ion formed from the reaction of t-butyl chloride with aluminum bromide. Such hydrogen transfers appear to be involved in many reactions of saturated hydrocarbons.

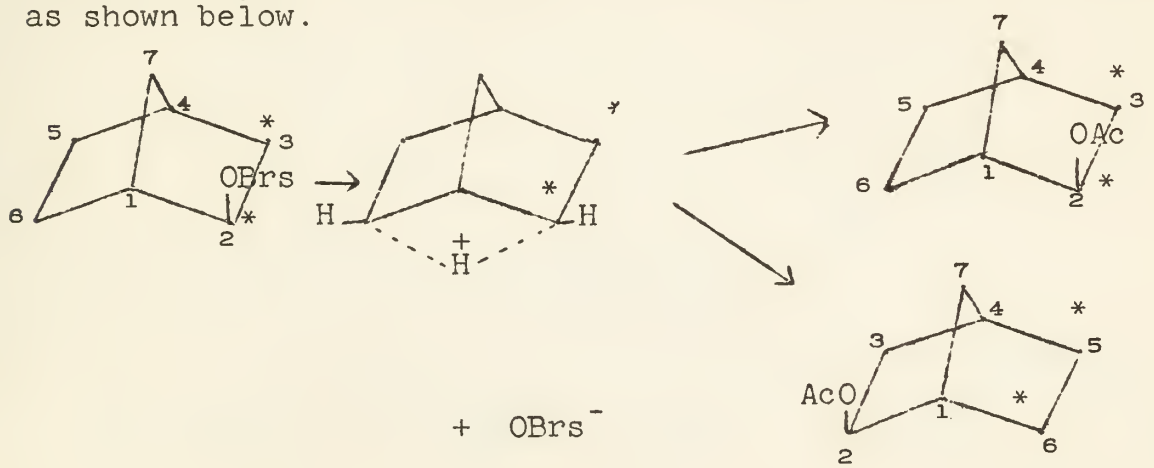
$$(CH_3)_3C\text{-}Cl + AlBr_3 \rightleftharpoons (CH_3)_3C^+ + AlClBr_3^-$$

$$(CH_3)_3C^+ + H\text{-}C\begin{matrix}(CH_3)_2\\C_2H_5\end{matrix} \rightleftharpoons (CH_3)_3C\text{-}H + {}^+C\begin{matrix}(CH_3)_2\\C_2H_5\end{matrix}$$

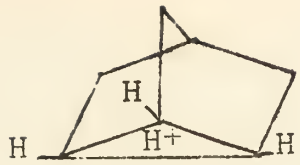
$${}^+C\begin{matrix}(CH_3)_2\\C_2H_5\end{matrix} + AlBr_3Cl^- \rightleftharpoons BrC\begin{matrix}(CH_3)_2\\C_2H_5\end{matrix} + AlBr_2Cl$$

The present seminar will deal with hydrogen transfers which, although similar to that above, occur under conditions so mild as to be peculiar to cyclic systems.

Bicyclic Systems.--- The solvolysis of optically active exo-norbornyl p-brombenzenesulfonate in glacial acetic acid to give optically inactive exo-norbornyl acetate has been explained as a Wagner-Meerwein rearrangement with a symmetrical bridged ion intermediate.[2] Roberts and Lee,[3] however, examined the solvolysis of exo-norbornyl p-brombenzenesulfonate labeled with C^{14} in the 2- and 3-positions and found that considerable C^{14} was distributed in the 5- and 6-positions in the resultant acetate. Their results appear to require that about 30% of the reaction proceed with hydrogen transfer from the 6-to the 2-position through a symmetrical intermediate ion as shown below.



Roberts has preferred the alternative formulation of this intermediate as a "protonated cyclopropane."

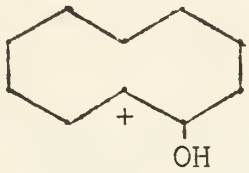


Doering and Wolf[4] have found evidence for a similar hydrogen transfer in the rearrangement of β-fenchol to β- and γ-fenchene and, more recently, Roberts and Yancey[5] and Vaughan and Perry[6] have shown that such a transfer occurs in the racemization of camphene with acids.

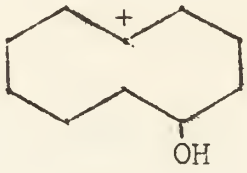
Medium-Ring Monocyclic Systems.--- Cope, Fenton and Spencer[7] observed that performic acid oxidation of cyclooctene lead not only to the expected trans-1,2-cyclooctanediol but also to a 26% yield of an isomeric glycol which was shown to be 1,4-cyclooctanediol. Furthermore, cyclooctene oxide, the suspected intermediate in this unusual reaction, was observed to yield a similar glycol mixture when treated with formic acid.

The reaction has been extended by Prelog, Schenker and Küng[8,9] who obtained the following results. Cycloheptene gave only normal 1,2-glycol.[8] cis- and trans-Cyclononene each gave a mixture of the two diastereoisomeric 1,5-glycols and none of the normal 1,2-product could be found.[8] The most significant results were obtained with cis- and trans-cyclodecene.[9] In this case the cis-olefin gave one diastereoisomeric 1,6-cyclodecanedio while the trans- gave the other. None of the normal 1,2-product was observed.

These last results appear to exclude ionic intermediates of the type (A) or (B), since the cis- and trans-olefin would each give the same ion and, hence, the same product mixture. Both Cope and Prelog have suggested that the reaction proceeds

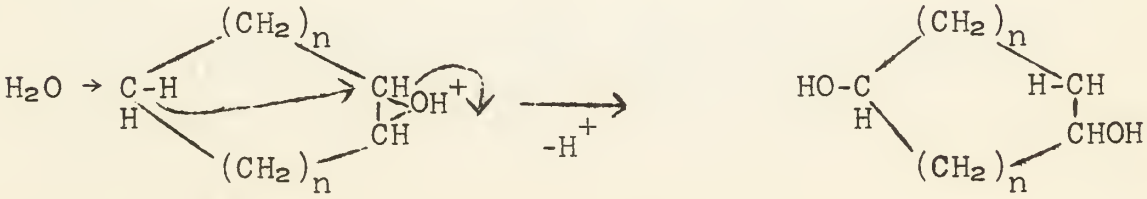


(A)



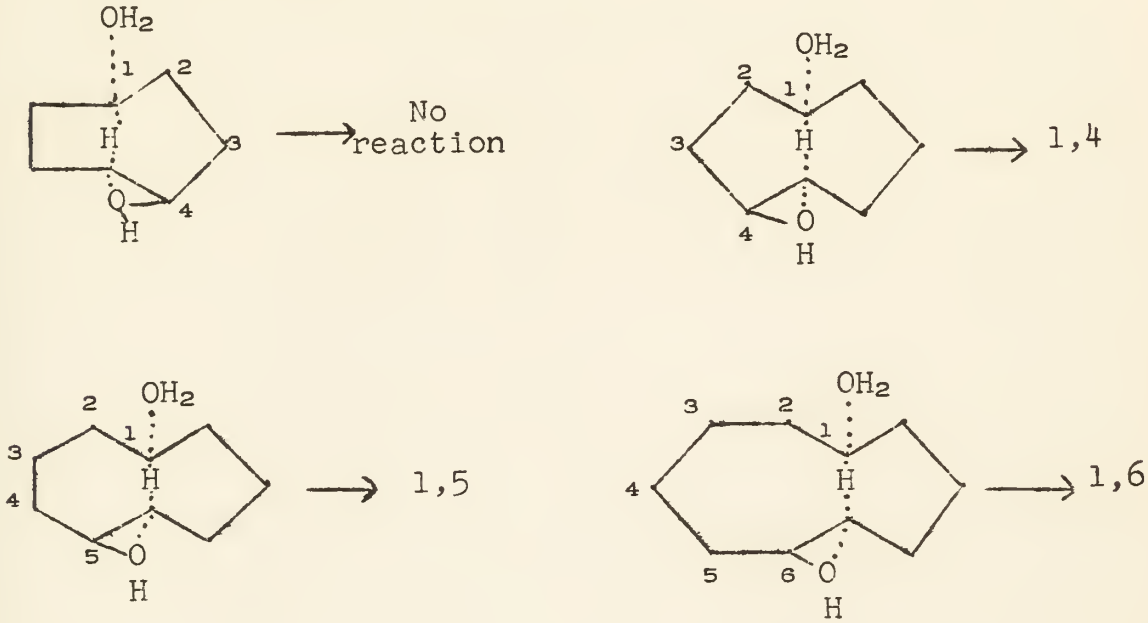
(B)

by the concerted process shown below.



The non-stereospecificity of the cyclononene reaction may be due either to the fact that it proceeds by a different mechanism or to prior isomerization of the starting olefins by formic acid. All of these reactions are complicated by the formation of appreciable amounts of other products some of which have not yet been identified.

With the limited data available a tentative generalization about the reaction can be formulated by comparing the transition states.



It can be seen in each case that hydrogen is transferred in such a way that it is always contained in a six-membered cycle (the right-hand ring as drawn here). Examination of models suggests that this rule is strictly an empirical generalization and may be more valuable as an aid to memory than as a way of predicting results of the reactions of compounds not yet studied.

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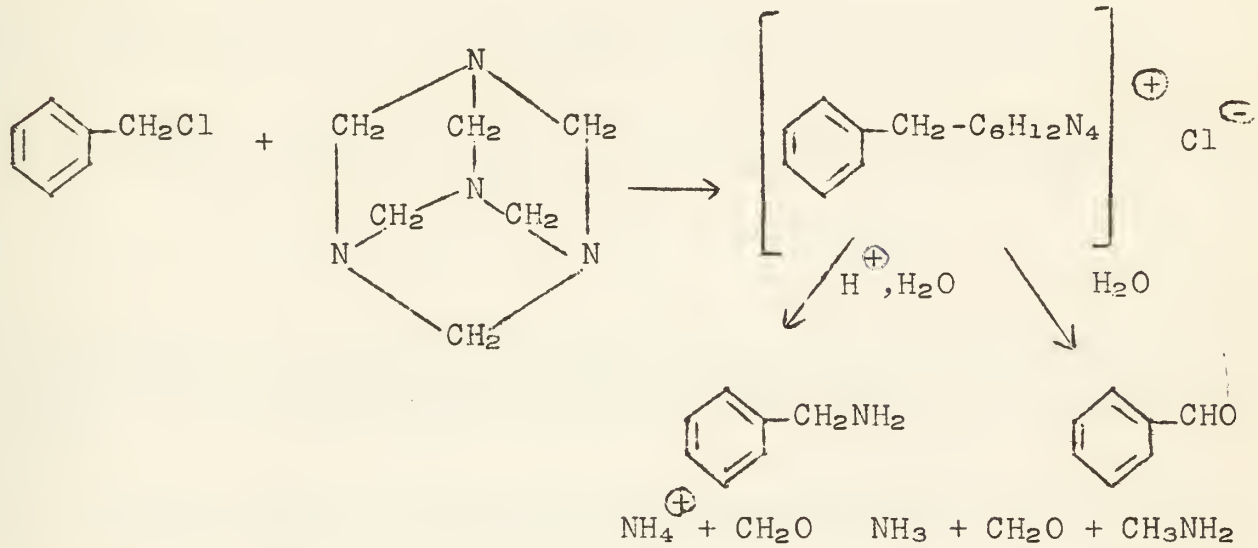
On the Mechanism of the Sommelet Reaction

Reported by L. E. Miller September 25, 1953

The conversion of certain amines, halides or salts formed from halides and hexamethylenetetramine (hexamine) to aldehydes in the presence of hexamine (or ammonia and formaldehyde) is called the Sommelet reaction.[1]

The hexaminium salts which can be isolated if prepared in an anhydrous solvent such as chloroform[2] are hydrolyzed by an excess of strong acid to a primary amine, ammonia and formaldehyde. This constitutes an excellent method for the preparation of primary amines.[3] In the presence of water these quaternary salts are unstable and decompose on heating to give an aldehyde, formaldehyde, ammonia and its methylated products.[4]



This reaction is general for the preparation of aromatic aldehydes, and can be used for the preparation of a number of aliphatic and heterocyclic aldehydes.

Aldehyde	Yield	Ref.
o-ethylbenzaldehyde	34%	5
2-naphthaldehyde	80%	6
n-heptaldehyde	50%	7
trimethylacetaldehyde	59% (80%)	7
3-formylpyridine	57%	8
4-formylisoquinoline	50%	8
4-formyl-2-phenylthiazole	56%	8

It is interesting to note that Sommelet published no experimental details but in 1914 a patent was issued.[9]

Isolation of the quaternary salt is unnecessary; the halide can be heated with hexamine in water, aqueous ethanol or best in 50% acetic acid.

Aliphatic aldehydes cannot be prepared by the usual Sommelet reaction starting either with the amine or the halide.

Under these reaction conditions any aldehyde which might be formed undergoes complex condensation reactions. When n-heptaldehyde was submitted to these conditions for two hours only traces of it were recovered. Since alkyl halides react slowly with hexamine, the hexaminium salts were isolated first. Though hexamine is necessary for the Sommelet reaction it promotes the side reactions with aliphatic aldehydes. By carrying out the reaction between the hexaminium salts with hexamine in 50% acetic acid into which a stream of steam was passed, the aldehydes were removed as fast as they were formed.

In a similar manner, electron attracting substituents on aryl methyl halides decrease the rate of formation of hexaminium salts. The conversion of these salts to aldehydes is not effected by such substituents but gives yields which are at a maximum at a definite reaction time and drop off sharply on prolonged heating. If the hexaminium salts are prepared in chloroform and isolated this difficulty is overcome.[10]

Sommelet suggested that the first step in the decomposition of the hexaminium salt involved the formation of an imine:

$$[ArCH_2C_6H_{12}N_4]^{\oplus} \; Cl^{\ominus} \rightarrow \underset{\text{I}}{ArCH_2\text{-}N{=}CH_2}$$

A decomposition of this type would explain those cases in which an aldehyde is not formed because of steric hindrance[11,12]. A polymer of the methyleneamine is the main product of the reaction.

At the pH of the reaction (3-6) methyleneamines I are in equilibrium with the corresponding amine:

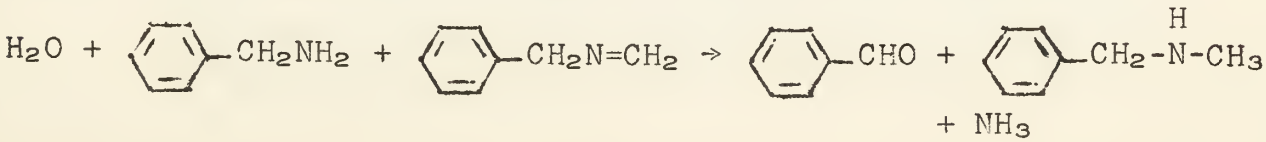
$$ArCH_2\text{-}N{=}CH_2 + HOH \rightleftarrows ArCH_2NH_2 + CH_2O$$

Thus if a compound such as I is an intermediate it should give an aldehyde under the conditions of the Sommelet reaction. It has been found[13] that methylenebenzylamine (or a mixture of benzylamine and formaldehyde) can be converted into benzaldehyde in good yields by means of hexamine.

The necessity of using hexamine in this conversion shows that the role of hexamine is not restricted to quaternary salt formation but that it has another part to play.

On studying the system benzylamine hydrochloride and formaldehyde in water, it was found that the low yield was due to the formation of benzylmethylamine in 50-65% yield. An amount of ammonia equivalent to the benzaldehyde was found.

Since the overall conversion of benzylamine into benzaldehyde and ammonia is an oxidation, it accounts for the reduction of an equivalent amount of methylenebenzylamine:



Presumably benzylamine is first dehydrogenated to benzaldimine,

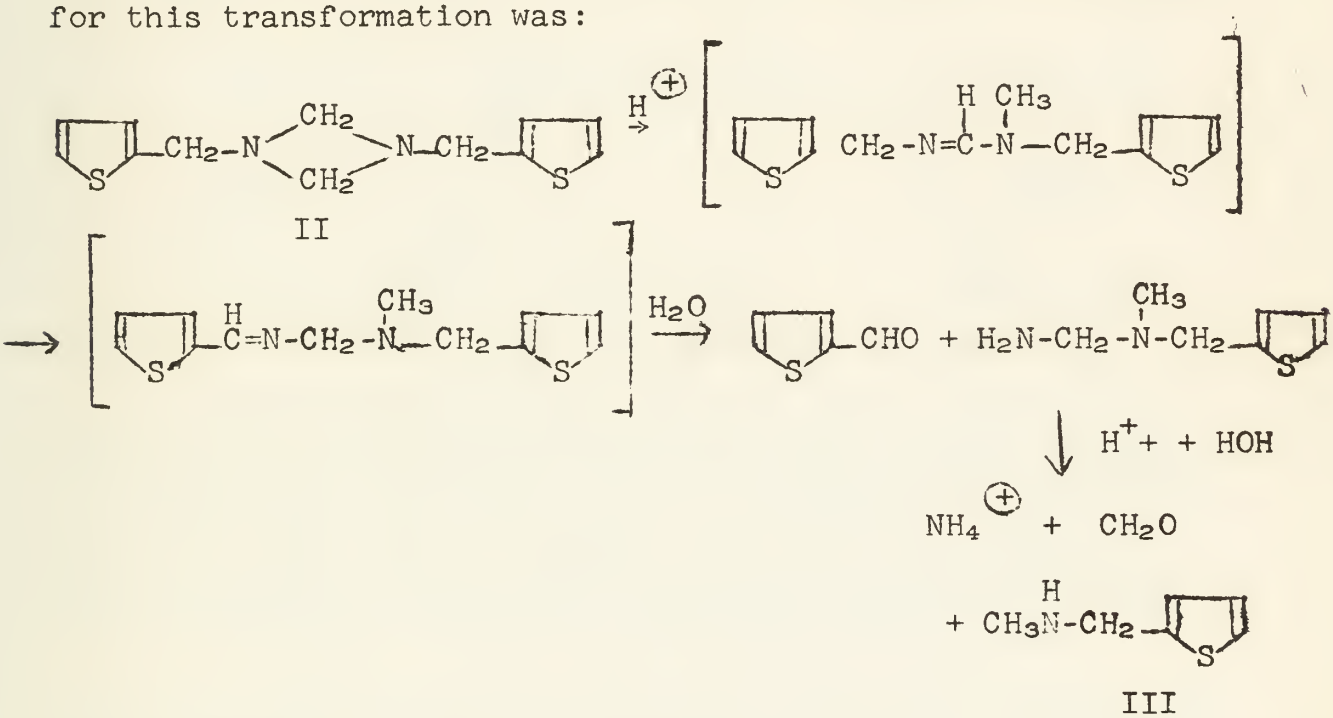
-CH=NH and this is hydrolyzed to benzaldehyde.

The yield of aldehyde in the absence of hexamine is limited by the conversion of an equivalent amount of benzylamine into benzylmethylamine.

When hexamine is used as the hydrogen acceptor the methylation of benzylamine is repressed, methylamine is formed instead from "methyleneimine $CH_2=NH$", an hydrolysis fragment of hexamine.

Thus for preparative purposes, the ratio of hexamine to benzylamine should be kept high. Under otherwise identical conditions benzyl chloride with 1,2 or 3 moles of hexamine gave 70, 77 and 80% yields of benzaldehyde. When benzyl chloride was added dropwise to a boiling solution of hexamine in water yields of over 80% were obtained.

It has been reported[16] that the "dimer" of N-methylenethienylmethylamine II underwent hydrolysis at pH 3 to 6.8 to give 2-formylthiophene and N-methyl-α-thienylmethylamine III. This is the Sommelet reaction. The mechanism, proposed for this transformation was:



The objections to this mechanism are:

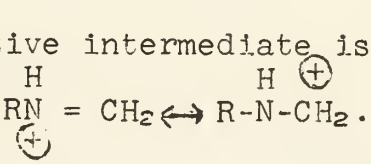
1). No dimer is present as shown by precise molecular weight studies. Even if it could be present in equilibrium it would not likely have the diazabutane ring, a structure which has never been established for any compound. The trimer, which is present, is generally believed to have the relatively stable 1,3,5-triazine ring.

2). The second step includes the prototropic rearrangement of an azomethine system which has been shown to occur only in a very strongly basic medium[17] and is "in the highest degree unlikely"[18] under the slightly acidic conditions of the reaction.

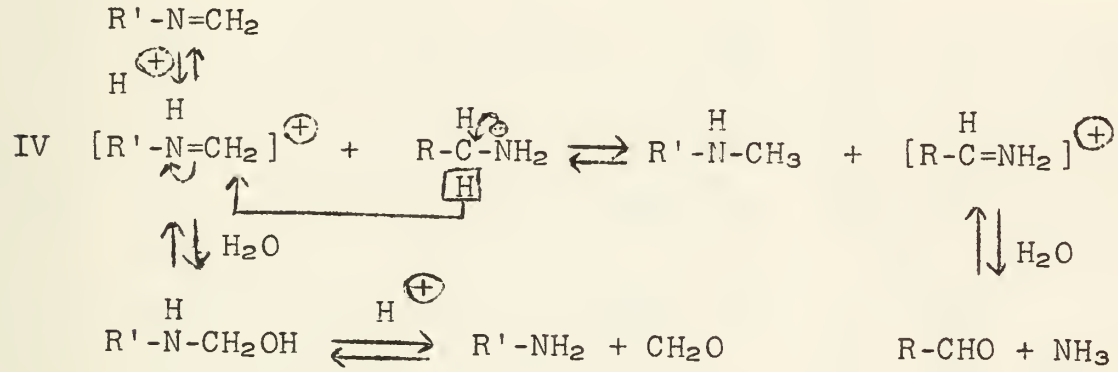
3). This mechanism allows only a 50% yield for the Sommelet reaction; they never obtained more. In the presence of hexamine and 50% acetic acid a 74% yield of 2-formylthophene is obtained either from 2-chloromethylthiophene or from 2-thienylmethylamine.

Angyl's Mechanism.

It is believed that the active intermediate is the conjugate acid of a Schiff's base



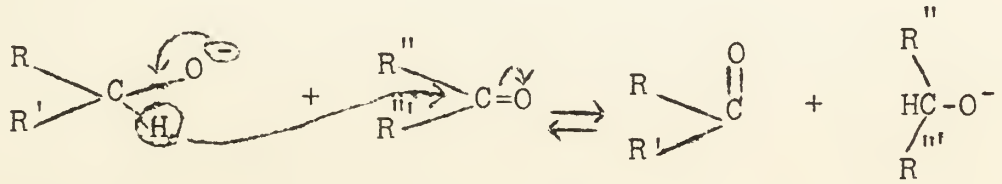
It is suggested that this mesomeric cation may attack amines.



In the most favorable case, when hexamine is used R'=H.

In aqueous solution the main reaction of the mesomeric cation will be hydrolysis according to the vertical scheme. This process is much faster than the Sommelet reaction, hence in strongly acid solution it goes to completion without descernible formation of aldehyde. Only in the pH range in which the amine and the methyleneamine are in equilibrium and IV is constantly reformed can the slower Sommelet reaction gain preponderance. Thus the pH limits are explained.

Since amines are ammono-alcohols and Schiff's bases are ammonocarbonyl compounds, this mechanism is the ammono-analog of Alexander's mechanism for the Meerwein-Ponndorf-Verley reaction.



In this system, owing to the strong electron-affinity of the oxygen atom, the carbonyl carbon atom is sufficiently electrophilic to attract the hydride ion, but the alcohol will not release it until its electron density has been increased by its transformation into an alkoxide ion.

On the other hand, in the ammono-system the amine releases the hydride ion (amines, when unionized, are readily oxidized) but the Schiff's base is not sufficiently electron attracting until converted into its conjugate acid. Thus the differing pH requirements for these two reactions.

This mechanism is compatible with all the known features of the Sommelet reaction.

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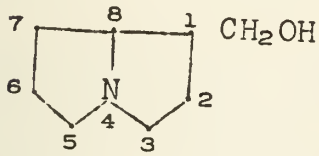
Stereochemistry of the Necines and Necic Acids in the Senecio and Related Alkaloids

Reported by Roger Adams

October 2, 1953

The alkaloids of several genera of plants from different families contain alkaloids of similar structural characteristics. The most important genera are Crotolaria, Heliotropium, Trachelanthus, Trichodesma and especially Senecio. The alkaloids have no useful pharmacological properties. They are toxic to animals, causing liver cirrhosis and poisoning of the lungs. The loss of cattle in West Texas is primarily due to consumption of Senecio longilobus.

The alkaloids are esters of aliphatic acids (called necic acids) with bases (called necines) which are bicyclic tertiary amines containing one or two hydroxyl groups. The alkaloids are also found in the form of their N-oxides. The necines thus far isolated are shown in I-V. The structures of all but V have been definitely established.[1] They are pyrrolizidine derivatives.



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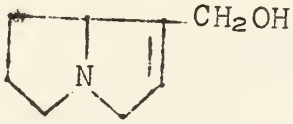

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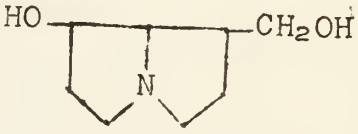

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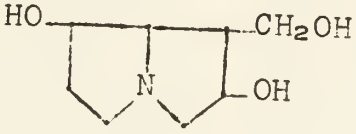

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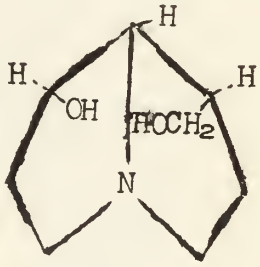

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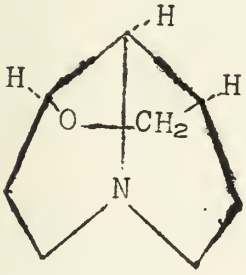

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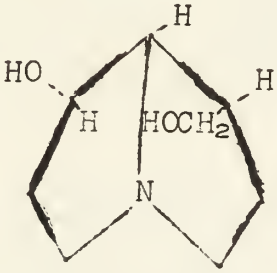

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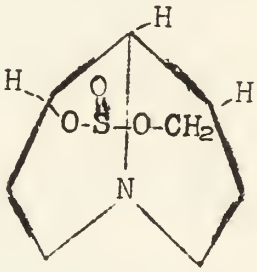


IX

The stereochemistry of these bases deserves consideration. Molecule I has two asymmetric carbon atoms, 1 and 8. Asymmetric C-8, however, can exist in only one configuration with the hydrogen atom behind the rings. Strains involved prevent C-8 from being in its enantiomorphic form. However, the two rings

are at an angle to each other which inducesmolecular asymmetry. As a consequence of the asymmetry at C-1 and the molecular asymmetry, the molecule can exist in two racemic or four optically active forms. All forms of structure I are known. Structure III which has an additional asymmetric carbon atom, C-7, may therefore exist in four racemic or eight optically active forms. Formula VI represents a geometric structure of formula III.

Dr. Leonard[2] deduced that in compound III the hydroxymethyl group is trans to the hydrogen at C-8. His arguments were based on the fact that III forms an anhydride with great ease by treatment with a variety of dehydrating agents. The anhydroplatynecine formed can have only one structure, VIII, as determined by the study of models. He postulated it to be very unlikely that the reagents would cause inversion at C-1 but that they might or might not cause inversion at C-7; hence in III or VI, the CH_2OH group is trans to the hydrogen at C-8. Related degradation products such as ℓ-heliotridane in which compound III has had both hydroxyls replaced by hydrogens is assumed to have the same configuration at C-1.

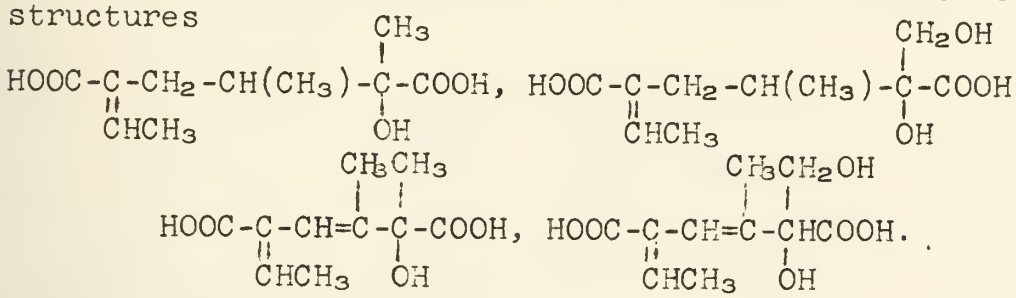
The ease of dehydration of VI to the anhydro derivative VII suggests the probability that the hydroxyl at C-7 is cis to the hydroxymethyl group in platynecine. Dr. Van Duuren has established this and has demonstrated that ordinary reagents do not invert the hydroxyl at C-7. He compared the action of certain reagents on dihydroxyheliotridane (VIII) and platynecine (VII). Previous degradation studies[3] have demonstrated that the hydroxymethyl group in each compound is trans to the hydrogen atC-8. It may therefore be assumed that in dihydroxyheliotridane (VIII) the hydroxyl at C-7 is trans to the C-1 hydroxymethyl and cis to the hydrogen at C-8. Attempts to dehydrate dihydroxyheliotridane (VIII) under the same conditions that caused dehydration of platynecine (VI) to anhydroplatynecine (VII) failed. Thionyl chloride at 0° produced from compound VI a cyclic sulfite (IX) from which platynecine VI could be recovered by hydrolysis.[4] Models indicate that only with structure VI is such a cyclic sulfite possible. Compound VIII by similar treatment is converted to a chloro hydrin in which the C-7 hydroxyl is replaced by chlorine. The diacetates of VI and VIII, prepared by the action of boiling Ac_2O, both hydrolyzed to the respective dihydroxy compounds.

Two stereoisomers of compound IV have been found in these alkaloids.[1] They differ merely at the C-7 where in one isomer the hydroxyl is cis (retronecine) and the other trans (heliotridine) to the hydrogen at C-8. These isomers are catalytically reduced stereospecifically to give in the former case compound VI and in the latter case compound VIII.[2,5]

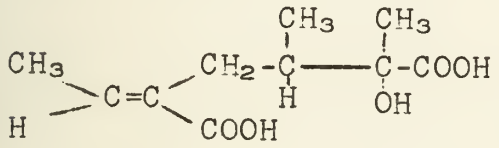
Base I is found in the alkaloids esterified with monobasic acids.[1] Base VIII and base IV with the C-7 hydroxyl cis to the hydrogen at C-8 are also found esterified only with monobasic acids on the hydroxymethyl group. Base VI, however, and base IV with the C-7 hydroxyl trans to the hydrogen at C-8 are always found as esters with dibasic acids (X). These are

large ring compounds of 12 or 13 atoms. It is noteworthy that structural models of these large ring compounds can be built satisfactorily only with the configurations of the bases as previously described.

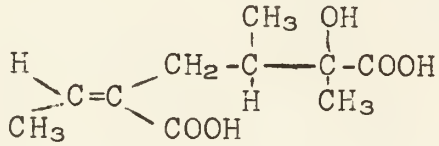
The stereochemistry of certain of the acids with ten carbon atoms found particularly in the Senecio alkaloids will be discussed here.[6] Degradation studies of four closely related acids have shown these acids to have the following structures



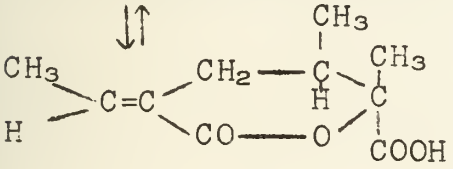
The stereochemistry of the first one has been carefully studied. It has one double bond and two asymmetric carbon atoms and consequently may exist in 4 racemic modifications or ~~16~~ 8 optically active forms. Four of these forms, in which the β-carbon atom holding a hydrogen and methyl group has a fixed configuration, have been isolated. All give the same lactone by dehydration but two are lactonized more readily than the others. The infrared and ultraviolet spectra serve to distinguish between the cis and trans configurations at the double bond. Hence, the structural formulas are established;



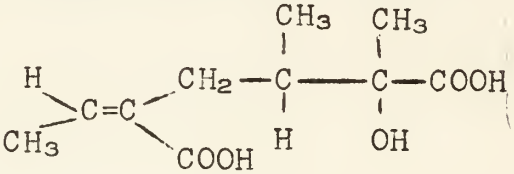
trans-cis
Integerrinecic acid (m.p. 151°)



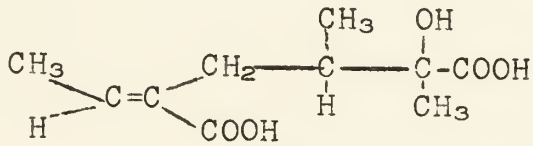
cis-trans
Senecic acid (m.p. 151°)



trans-cis
Integerrinecic acid lactone

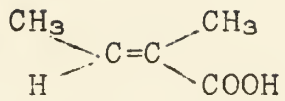


cis-cis
Usaramoensinecic acid (m.p.170°)

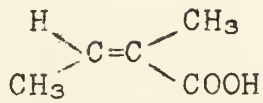


trans-trans
Platynecic (Hieracinecic) acid (m.p. 133°)

Spectra



tiglic (trans)



angelic (~~trans~~) cis

Infrared ($CHCl_3$ soln.)

Acids	Geom. Conf.	C=C Absorp.	Intensity	U.V. (C_2H_5OH) max (m μ)	ε max
Angelic	cis	1645	med-strong	216	9,500
Tiglic	trans	1650	strong	212	13,500
Usaramoensinecic	cis	--	--	215	5,977
Senecic	cis	1635	very weak	215	6,185
Integerrinecic	trans	1645	strong	214	9,021
Hieracinecic	trans	1657	strong	213	10,760

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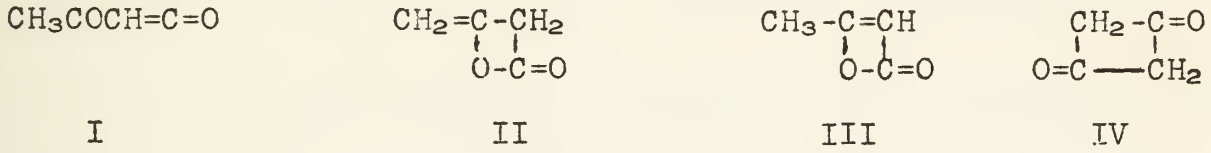
6. Warren et al., J. Chem. Soc., 2856 (1949); 700 (1950); 1700 (1949); 1703 (1949); Adams, Hamlin, Jelinek and Phillips, J.A.C.S., 64, 2700 (1942); Adams, Govindachari, Looker and Edwards, ibid., 74, 700 (1952), Adams and Van Duuren, unpublished results.

RECENT CONTRIBUTIONS CONCERNING THE STRUCTURES AND REACTIONS OF KETENE DIMERS

Reported by H. R. Snyder October 2, 1953

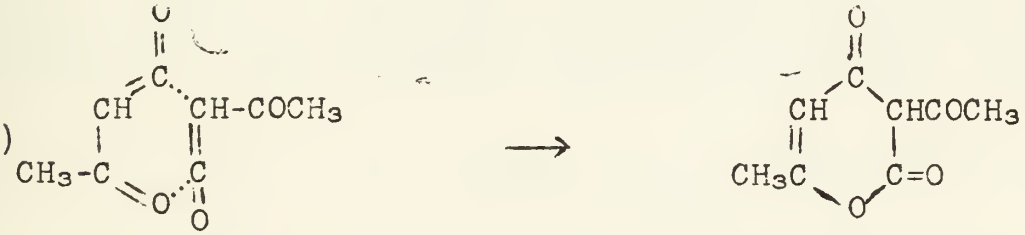
Ketenes[1] are substances containing a carbonyl group the carbon atom of which is also part of an olefinic linkage; thus they have the functional group -C=C=O. The simplest member, called ketene, CH_2=C=O, is prepared industrially by the pyrolysis of acetone or acetic acid as an intermediate in the production of acetic anhydride, propiolactone and isopropenyl acetate. The higher homologs are classified as monosubstituted (RCH=C=O, sometimes referred to as aldoketenes) and disubstituted (R_2C=C=O, sometimes referred to as ketoketenes) ketenes. All known ketenes change to dimers and in some cases polymers, upon standing or upon being heated. The dimer of ketene, usually called diketene, is a liquid of harsh, irritating odor and of chemical properties very similar to those of ketenes or acid anhydrides. The dimers of disubstituted ketenes, on the other hand, have the properties of ketones. Most of the known dimers of monosubstituted ketenes are chemically similar to diketene, but in certain instances two dimers are known; thus methylketene forms a liquid dimer which resembles diketene and a solid isomer which resembles the dimer of dimethylketene. The question of the structures of the ketene dimers has been under investigation for some forty years.

Most of the interest in the structural problem has centered around diketene, probably as a result of its ready availability and its use as a source of acetoacetic acid derivatives. It is converted to methyl acetoacetate by the action of methanol and a trace of mineral acid and to acetoacetanlide by the action of aniline. Heated alone it dimerizes to dehydracetic acid. Of the four principal structures which have been considered (I-IV) the first provides the simplest representation (equation 1) of the change to dehydracetic acid, and for this reason was long preferred by many chemists. On the basis of this structure the



I II III IV

(1)

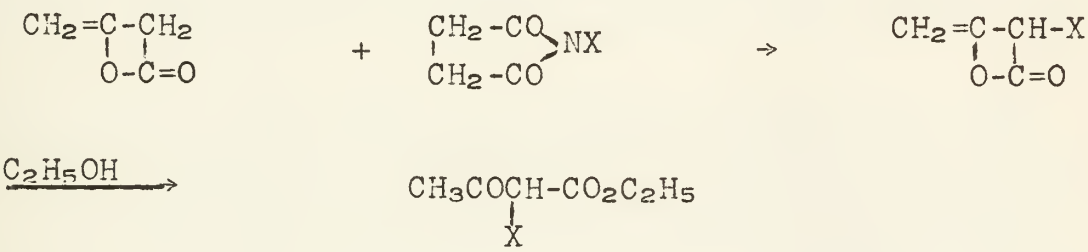


Dehydracetic acid

conversion of diketene to esters and amides of acetoacetic acid would be represented as ordinary reactions of a ketene, proceeding by addition of active hydrogen functions to the carbonyl group. Formulas II and III are recognized as the lactones related to the two possible enols of acetoacetic acid. Conversion of either of these structures to acetoacetic acid derivatives by alcohols or amines could be viewed as simple alcoholysis or ammonolysis reactions.

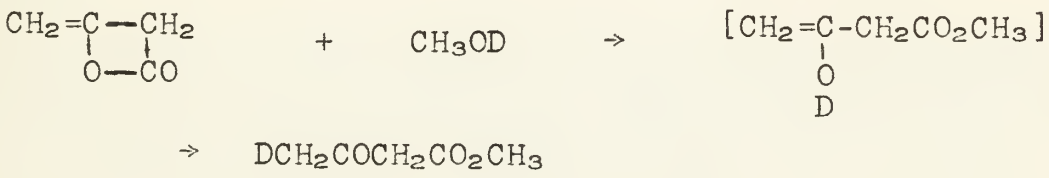
In 1946 Whiffen and Thompson[2] concluded, from studies of the infrared absorption spectra of liquid diketene and its solutions, that the acetylketene formula (I) is untenable, and Miller and Koch[3] reached the same conclusion in similar studies with the vapor. The latter authors expressed the opinion that an equilibrium between the two lactone formulas (II and III) provided the best representation of diketene. In studies of the Raman spectrum of liquid diketene Taufen and Murray[4] concluded that the crotonolactone formula (III) and the cyclobutane structure (IV) were unacceptable, and Bregman and Bauer[5] reported that formulas I and IV could be excluded on the basis of electron diffraction studies of the substance in the vapor state. Thus the physical studies seem to determine the structure of diketene as 3-butenoic β-lactone (II).

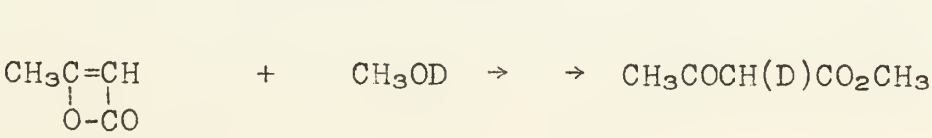
Chemical evidence in support of structure II recently has become available.[6,7,8] In studies of the Ziegler allylic halogenation of diketene and ethanolysis of the halogen derivatives Blomquist and Baldwin obtained only α-haloacetoacetates (equation 2). Allylic halogenation of structure III would be expected to result in γ-haloacetoacetic acid derivatives. In

(2)


a re-examination of the ozonolysis of diketene Hurd and Blanchard[7] demonstrated the production of formaldehyde and malonic acid, and could find no indication of the production of pyruvaldehyde. Thus structure II is indicated.

The most recent chemical contribution is the result of study of the reaction of diketene with deuteromethanol (CH_3OD) by Johnson and Shiner.[8] As can be seen in equations 3 and 4 the reaction applied to structures II and III should give isotopically different methyl acetoacetates containing deuterium. The methyl acetoacetate formed by either path will, of course, have an

(3)


(4)


opportunity to exchange with the deuteromethanol, so it was necessary to determine the course of such an exchange under the conditions to be used with diketene. Preliminary experiments with methyl acetoacetate and deuterium oxide, carried out at 25° over periods ranging from 15 minutes to 65 hours, showed that 1.90 ± 0.02 atoms were exchangeable. This leads to the conclusion that only the α-hydrogen atoms are exchangeable under the conditions used. Exchange between methyl acetoacetate and deuteromethanol was slower, but in one hour at reflux the value was 1.86, again supporting the view that only the α-hydrogen atoms are involved.

If it is true that only the α-hydrogen atoms are exchanged, it should be possible to "wash out" the deuterium from the ester $CH_3COCH\text{-}(D)CO_2CH_3$, or the similar di-α-deutero derivative, by refluxing it with successive portions of ordinary methanol, but a γ-deutero derivative should lose little or none of its deuterium under such treatment. Also, it should be possible to analyze a methyl acetoacetate for γ-deuterium in two ways. These are by substraction of exchangeable (α) deuterium from total deuterium as determined by combustion, and by determination of total deuterium after washing out of the α-deuterium. A methanolysis of diketene with deuteromethanol containing 82 mole % of deuterium gave a methyl ester having 0.73 atom of γ-deuterium, as determined by either analysis. Thus it seems clear that the methanolysis proceeds as represented by equation 3 above, and structure II is strongly indicated.

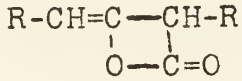
Information concerning the possible equilibrium between structures II and III also is available from this work. The uncatalyzed methanolysis of diketene is a rather slow process. In an experiment conducted at reflux over 85.5 hours with about 2.5 moles of deuteromethanol per mole of diketene the amount of diketene recovered was above 25%. Such diketene was found to contain deuterium. However, the exchange of hydrogen by deuterium in diketene is very much slower than the exchange in methyl acetoacetate. Furthermore, if a mobile equilibrum of II and III obtained in a medium containing active deuterium, one would expect rapid equilibration of all the hydrogen atoms in diketene. Actually, the recovered diketene contained deuterium only in the α-position.

These studies thus support the view that diketene is represented by structure II only. Other recently published physical data (X-ray measurements on the crystalline solid[9] and electron bombardment in an analytical mass spectrometer) support the same view.

As indicated in the introductory paragraph above, there is little doubt but that the dimers of disubstituted ketenes are tetrasubstituted cyclobutanediones. Thus the dimer of dimethylketene is reduced to <u>cis</u> and <u>trans</u> glycols, and it yields a dioxime which is susceptible to the Beckmann rearrangement.[1] Monosubstituted ketenes evidently can dimerize in either way. The solid dimer of methylketene,[10,11] as well as that of ethylketene,[11] has been shown to be the cyclobutane derivative, the acidity being due to enolization. However, the liquid dimer of

methylketene behaved very much like diketene in reactions with deuteromethanol.[8] A mixed dimer related to methylketene and n-hexylketene and containing a tagged carbon atom (C^{14}) has been shown to have the lactone structure.[12] It appears that the dimers of monosubstituted ketenes prepared from acid chlorides and tertiary amines, in the procedure developed by Sauer[1,13] (equation 5), are of the lactone type. These dimers, being formed conveniently and in high yield, provide a valuable route from an acid RCH_2CO_2H to derivatives of the β-ketoacid $RCH_2COCH(R)CO_2H$.

(5) $RCH_2COCl + R_3N \xrightarrow{\text{ether}} [RCH{=}C{=}O] + R_3NHCl$

$\rightarrow$ 

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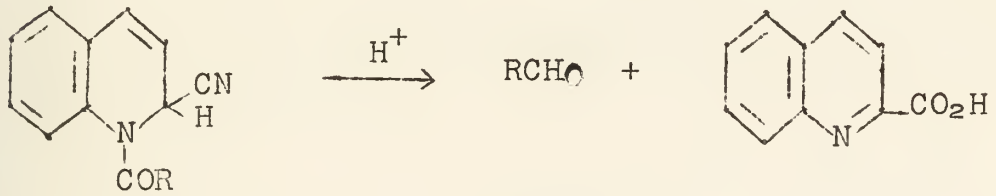
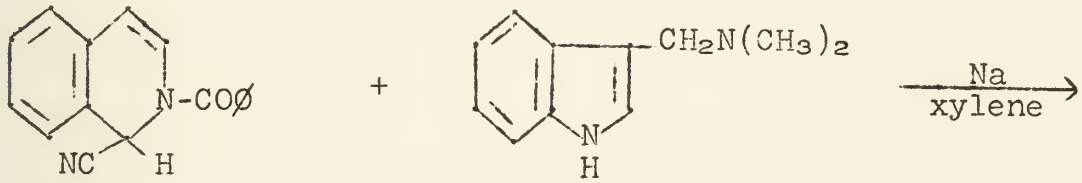
SYNTHETIC APPLICATIONS OF REISSERT COMPOUNDS

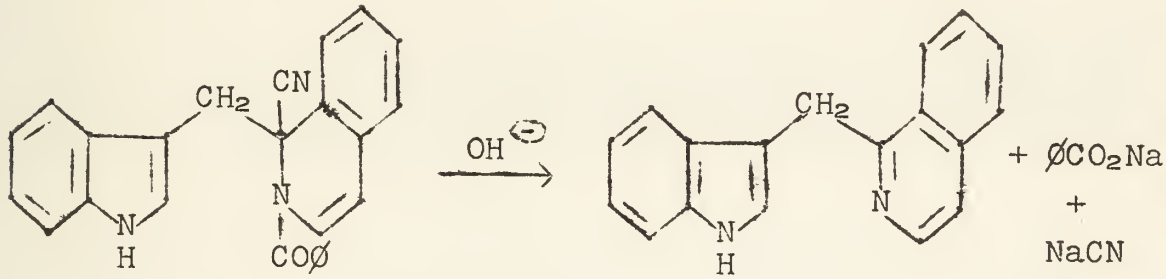
Reported by W. P. Samuels October 9, 1953

Reissert compounds[1] which may be prepared from acid chlorides and quinoline or isoquinoline in aqueous KCN, KCN in liquid SO_2, or liquid HCN in benzene have been useful for the conversion of acid chlorides to aldehydes[2].

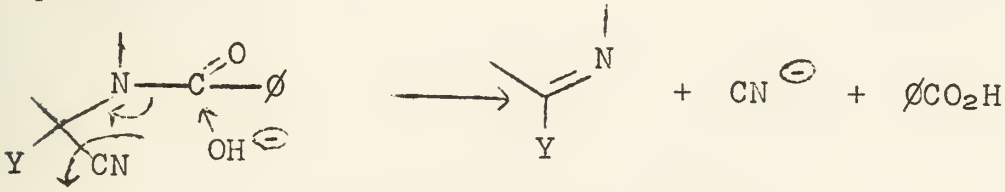


Recently Boekelheide[3,4,5] has developed methods for the synthesis of substituted quinolines and isoquinolines from Reissert compounds. One method involves the use of Mannich bases as the alkylating agents[3] and it may be illustrated by the synthesis of 1-skatyl-isoquinoline.

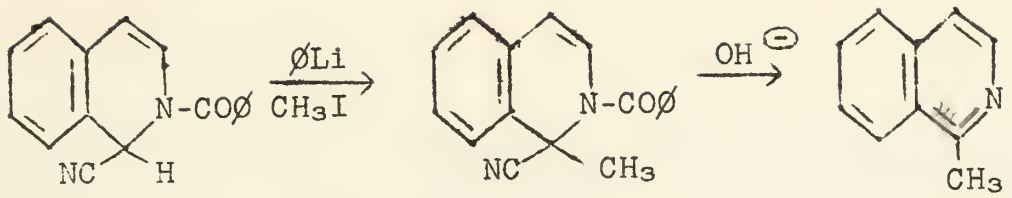




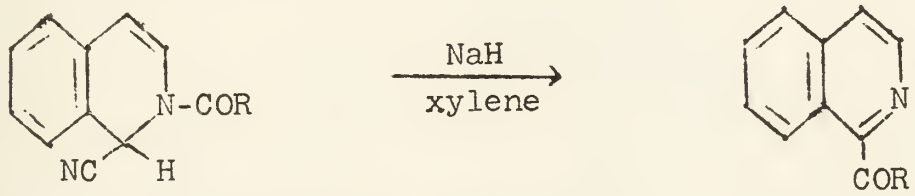
To explain the products resulting from alkaline hydrolysis and the ease of hydrolysis the following mechanism was proposed:



A second method has been effected by the use of various alkyl halides as alkylating agents[4] and it may be illustrated by the synthesis of 1-methylisoquinoline.

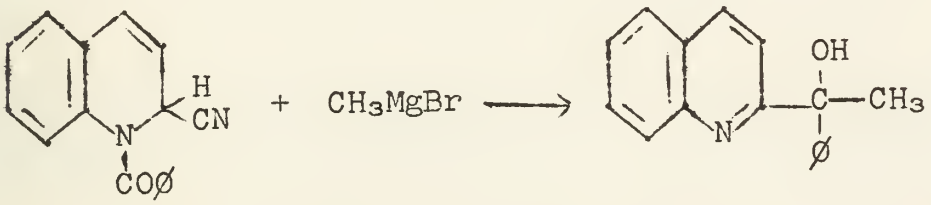


The conversion of the Reissert compound to its anion in the alkylation step must be carried out under mild conditions in order to obtain good yields; phenyllithium in an ether-dioxane mixture proved to be the most satisfactory reagent. If these proper conditions are not followed the reaction follows a different course which may be illustrated by the following equation:



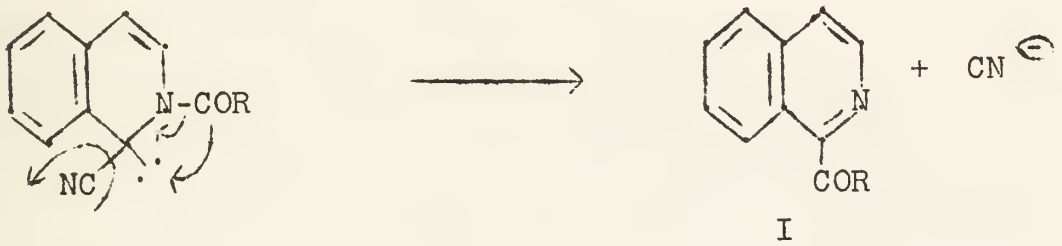
This rearrangement also occurred in the quinoline series.

A similar rearrangement has been reported by McEven and co-workers[6].



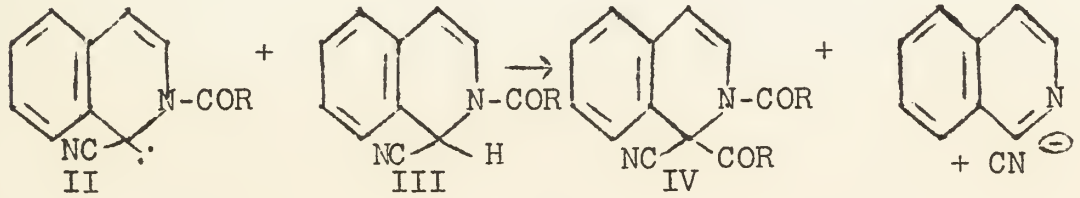
In both illustrations the important step is the rearrangement of the anion of the Reissert compound to the corresponding C-acyl heterocycle. An (A.) intramolecular or (B.) intermolecular process have been proposed as plausible mechanisms.

(A.)



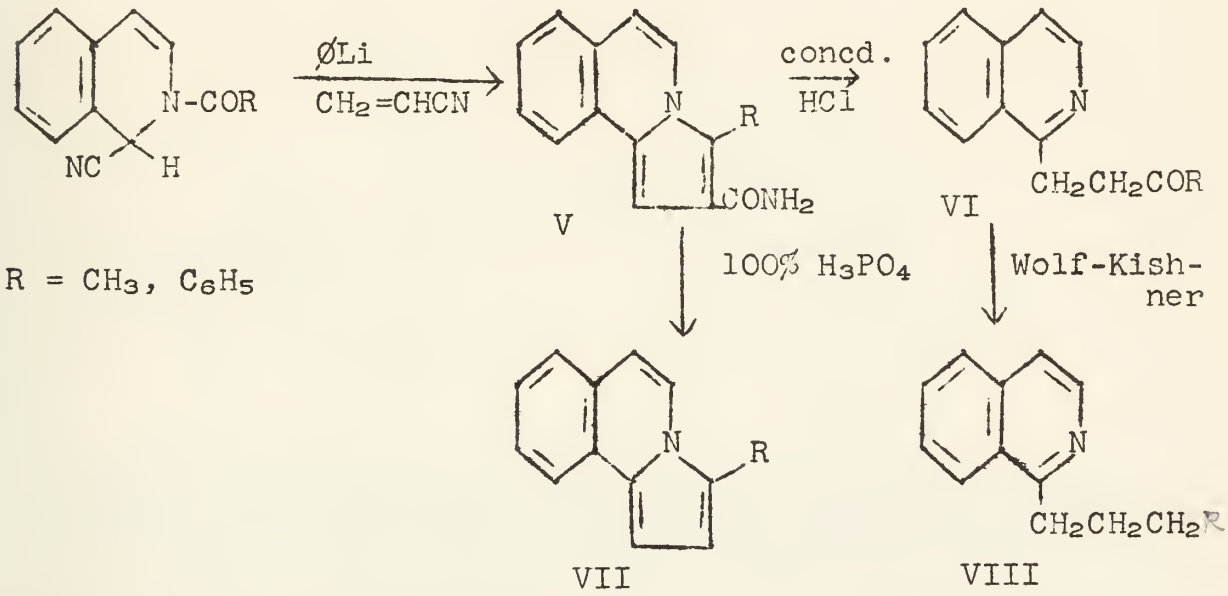
I

(B.) 1.



2. II + IV $\longrightarrow$ I + IV + CN^-

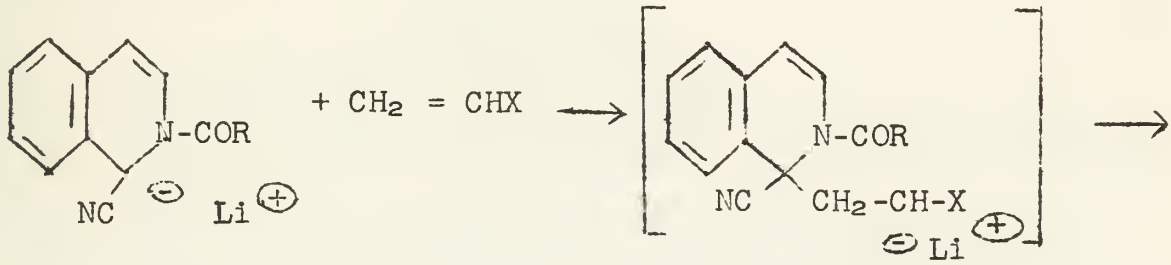
More recently Boekelheide[7] has investigated the use of Reissert compounds in condensations of the Michael type. In all cases studied condensation involved participation of the N-acyl group and resulted in rearrangement. A condensation may be illustrated by the reaction between 1-cyano-2-benzoyl-1,2-dihydroisoquinoline and acrylonitrile.



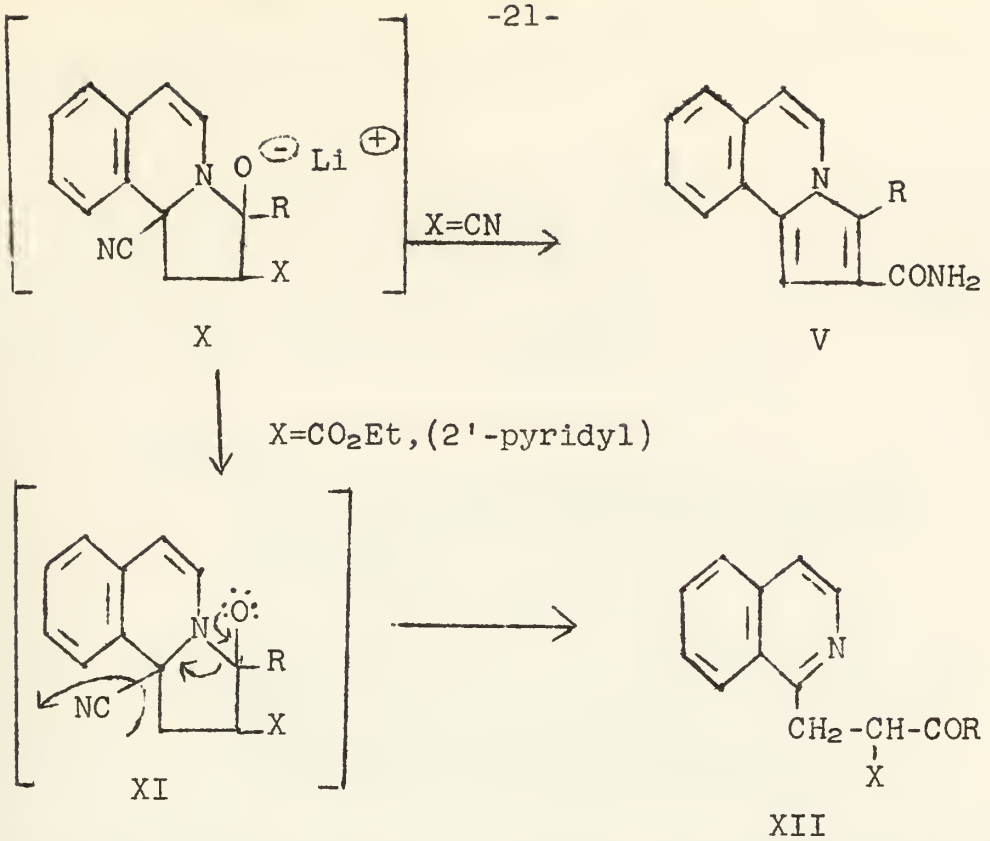
R = CH_3, C_6H_5

Hydrolysis of the amide group of V offers a simple and convenient method of synthesis of 7,8 benzopyrrocoline derivatives.

The use of ethyl acrylate or 2-vinylpyridine instead of acrylonitrile led to the formation of open chain ketones instead of the expected 7,8 benzopyrrocolines. To explain all these facts the authors proposed the reaction scheme shown below.



IX



As shown the formation of XII can be explained if it is assumed that X undergoes aromatization in a different manner. The reason for the group X being influential in determining the course of the reaction is not evident as yet.

It has been possible to convert VI, and XII to the corresponding benzopyrrocoline derivatives by cyclization using sulfuric acid or 100% phosphoric acid.

Thus Reissert compounds have been found to offer simpler methods of synthesis of substituted quinolines and isoquinolines, and 7,8-benzopyrrocoline derivatives.

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Hydrogen Transfer and Dehydrogenation

Reported by William R. Sherman October 9, 1953

As it is discussed here, hydrogen transfer is thought of as intermolecular hydrogen transfer, where covalently bound hydrogen atoms are removed from one organic molecule and transferred to another organic molecule, and dehydrogenation as the elimination of the removed hydrogen from the system as molecular hydrogen gas, or in some inorganic chemical combination such as H_2S or H_2Se.

I. Hydrogen transfer will be discussed under the topic headings:
   a. Metal-Catalyzed Disproportionation
   b. Metal-Catalyzed Hydrogen Transfer to Foreign Acceptors
   c. Uncatalyzed Transfers

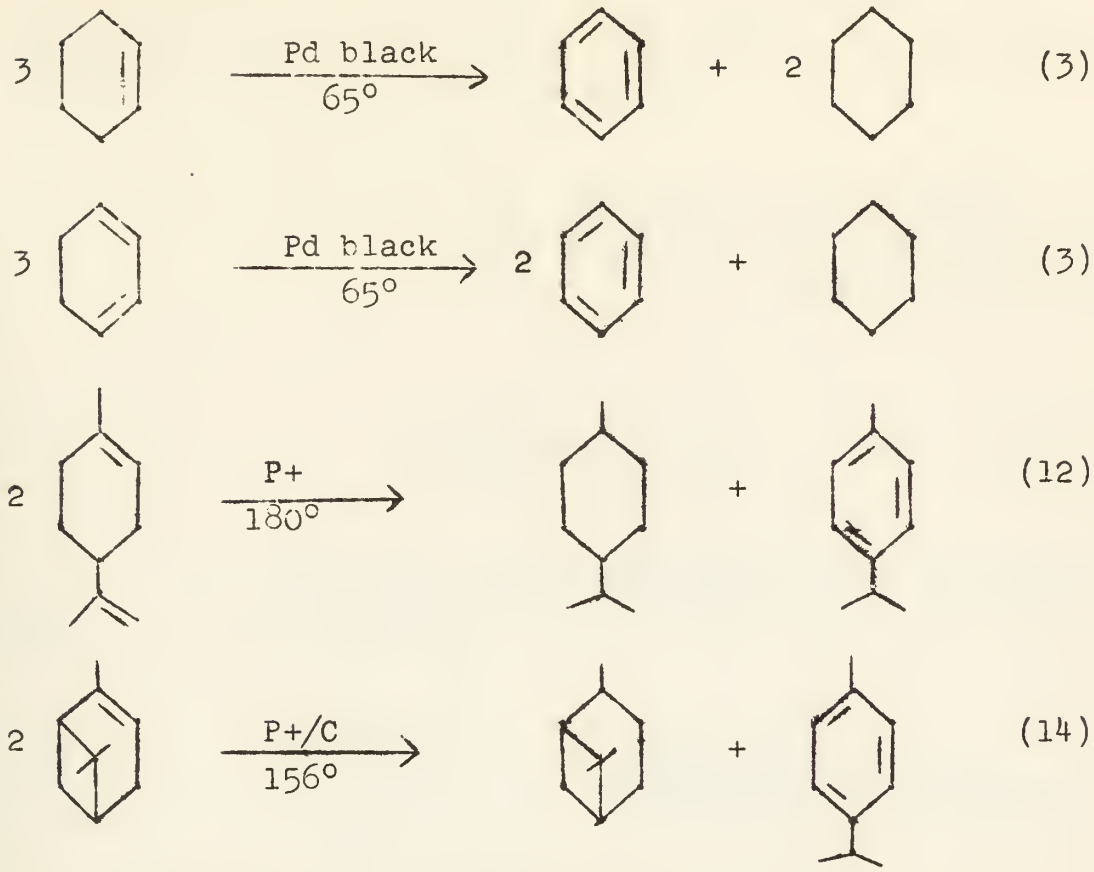
II. Dehydrogenation will be discussed under the topic headings:
   a. Thermal Dehydrogenations
   b. Metal-Catalyzed Dehydrogenations
   c. Chemical Dehydrogenations

In order to limit the paper, no attempt will be made to describe dehydrogenations of the oxidation variety, i.e., oxidations of alcohols to aldehydes, ketones etc.; discussion will be restricted to the removal of hydrogen to form C=C, C≡C, and C=N (in heterocyclic systems). The examples given are not necessarily generally applicable, and the use of a particular reagent is often dictated by the chemical stability of the compound under question toward a particular reagent, or by the thermal stability of the compound.

I. a. Disproportionation

Wieland[1] observed that 1,4-dihydronaphthalene undergoes disproportionation to naphthalene and tetralin at room temperature in the presence of palladium black. It was also observed[2] that under similar conditions both cyclohexadiene and cyclohexene disproportionate to cyclohexane and benzene. Linstead and co-workers[3] have confirmed the latter two reactions quantitatively, and have thrown some light on a fundamental question concerning them. The problem of whether a cyclohexadiene is an intermediate in the disproportionation of cyclohexene is considerably cleared by the finding that the concentration of 1,3-cyclohexadiene remains less than 1% throughout the reaction. This result plus the fact that both cyclohexene and cyclohexadiene disproportionate at comparable rates makes it probable that 1,3-cyclohexadiene is not an intermediate. Since 1,4-cyclohexadiene is even less likely as an intermediate, it seems probable that all four hydrogen atoms are removed simultaneously. Such a process could be pictured as termolecular, taking place on the catalyst surface, with one molecule of cyclohexene acting as donor and two molecules acting as acceptors.

The following examples illustrate disproportionation:



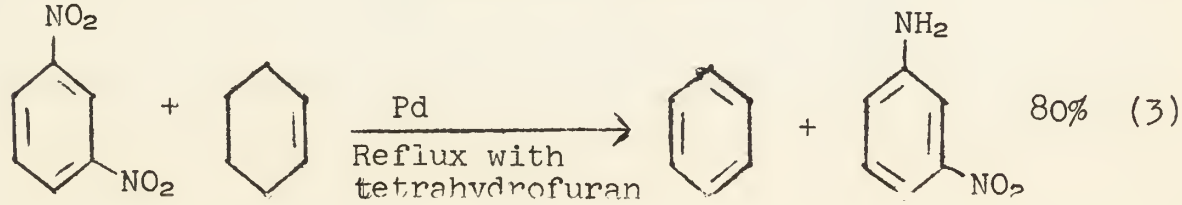
I b. Transfer to foreign acceptors

Linstead et.al.[3] have found that hydrogen transfer takes place between cyclohexene (and similar substances) as donor and a wide range of acceptors at temperatures below 100° in the presence of Pd catalysts (Pd black and Pd on charcoal). Acceptors studied include compounds containing ethylenic, acetylenic, azomethine, azo and nitro groups and certain activated carbonyls. The majority of the yields run from 90-100%.

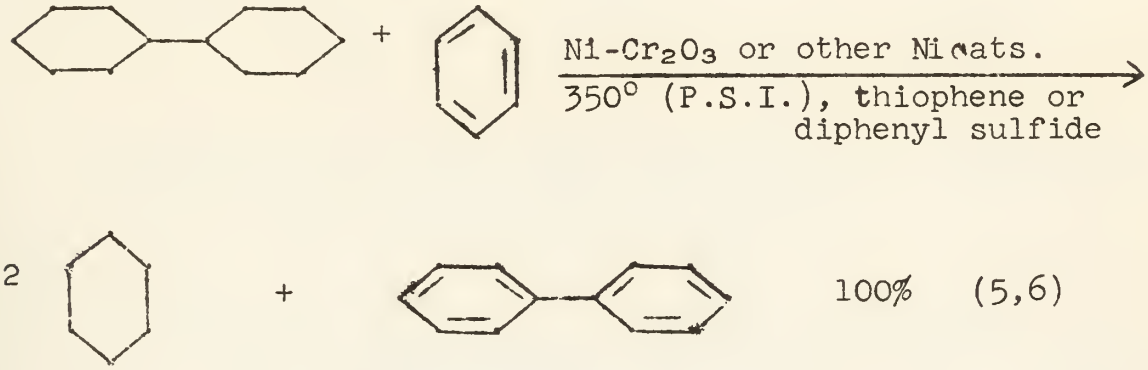
In quantitative studies it was shown that a foreign acceptor invariably slows down the rate of disproportionation, while non-acceptors have effects varying from no interference with disproportionation to complete stoppage.

In playing the role of a donor, the molecule giving up hydrogen often has an energy gain in resonance stabilization (about 40 Kcal/mol. in the case of hydroaromatic donors). The effectiveness of the donor depends on the acceptor, however, and no simple relationship between energy gain in going from hydroaromatic to aromatic system and effectiveness as donor is found.

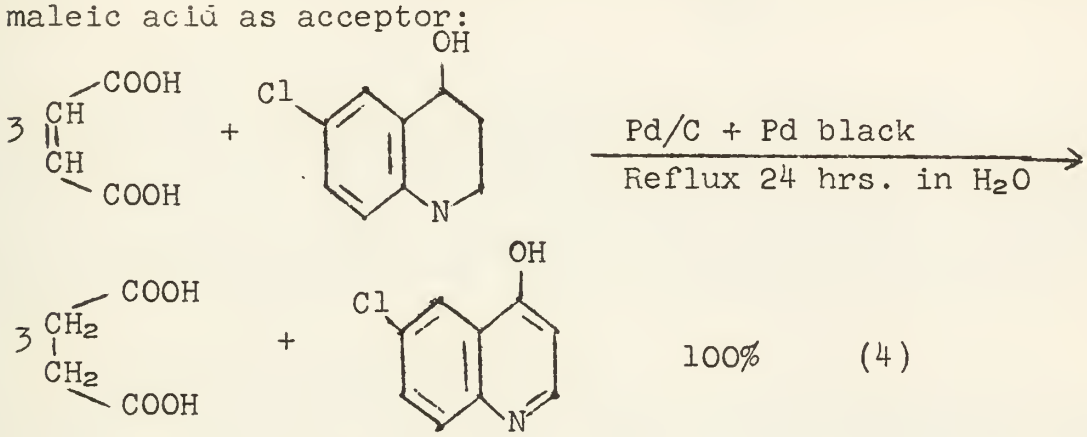
One example of Linstead's work is:



In studying the dehydrogenation of dicyclohexyl to diphenyl using benzene as acceptor and nickel catalysts, Adkins and co-workers[5,6] discovered that thiophene-free benzene inhibited the reaction, while the presence of thiophene or diphenylsulfide in a suitable proportion to the catalyst resulted in nearly quantitative yields.

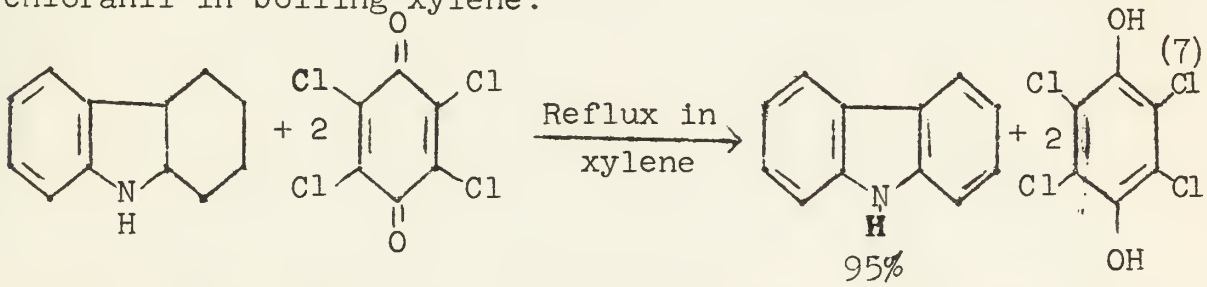


A recent application by Elderfield[4] is in the dehydrogenation of several tetrahydroquinolines and quinaldines using maleic acid as acceptor:



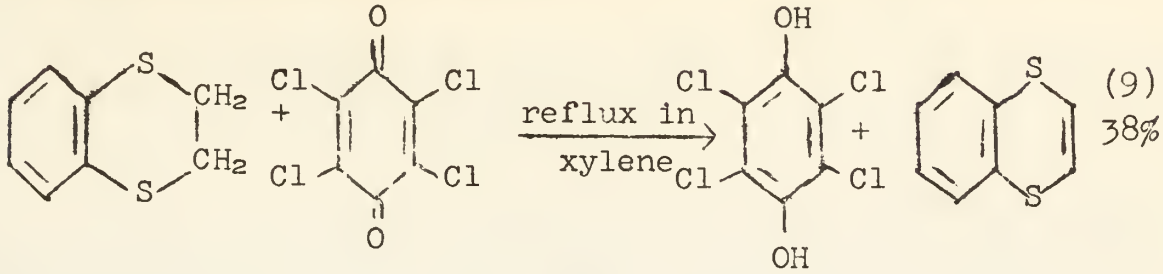
I. c. Uncatalyzed transfers

The use of various quinones as dehydrogenating agents has found considerable favor as a relatively low-temperature technique. The general procedure is to boil the compound to be dehydrogenated with the quinone in a solvent such as xylene, phenetole, cymene, etc., and isolate the dehydrogenated compound by precipitation of the hydroquinone with pentane.[19] The preparation of carbazoles from 1,2,3,4-tetrahydrocarbazoles has been shown to proceed smoothyl in 75-95% yields by use of chloranil in boiling xylene.[7]

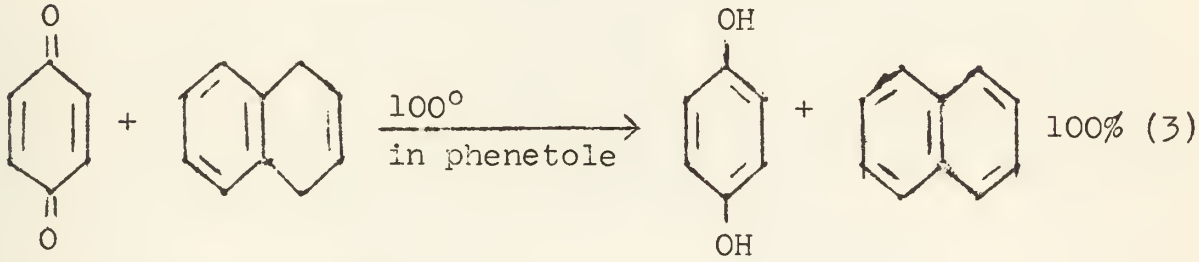


Bromanil has also been used in the preparation of carbazoles[8].

The dehydrogenation of benzo-1,4-dithiane was recently accomplished with chloranil[9]:



Linstead et.al.[3] have shown the quantitative aromatizatio of 1,4-dihydronaphthalene, using benzoquinone:



II. a. Thermal dehydrogenation

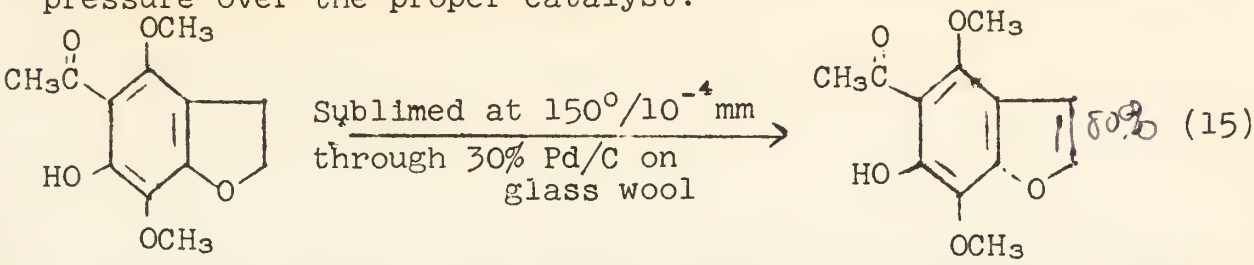
At sufficiently high temperatures, alkanes may be dehydrogenated to alkenes, alkadienes and alkynes without the use of catalysts. Considerable cracking of carbon-carbon bonds occurs and there is no selective production of alkenes or alkadienes. In some instances, this type of a mixed product may be desirable, but when a particular product is sought, catalysts are desirable.

II. b. Catalytic dehydrogenation

Catalytic procedures are often extremely selective, and cracking is kept at a minimum; thus in many important cases, catalytic procedures have found great industrial favor.

The range of catalysts which may be used to bring about dehydrogenations is far too great to be covered here. Generally, any catalyst which will serve as a hydrogenation catalyst will also be effective in a dehydrogenation role, pointing up the reversible character of catalytic hydrogenation. The primary difference between a catalytic reduction and a dehydrogenation is mechanical. Since the reactions on the surface of a catalyst are reversible, the hydrogen must be removed from the site of the catalyst to effect the dehydrogenation. Linstead et.al.[11,13,14] have shown that an excellent general procedure, using a Pt or a Pd catalyst, is to reflux the compound to be dehydrogenated in a suitable solvent, at 180 to 240° or more, while passing a stream of CO_2 or other inert gas through the mixture to carry the hydrogen away from the catalyst. Mechanical disturbances such as boiling are essential, and often a dehydrogenation may be carried out at a lower temperature by refluxing in a partial vacuum. Another technique is to pass the substance to be dehydrogenated over a catalyst at a suitable temperature in the vapor phase. Vapor-phase dehydrogenation may be used to advantage

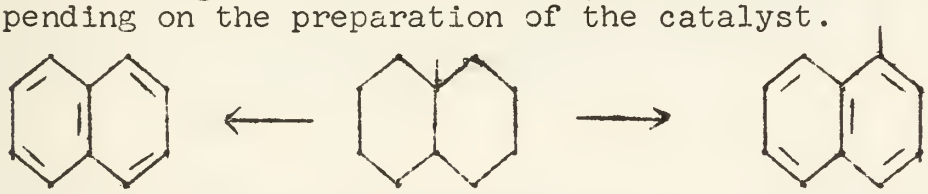
by subliming a compound at elevated temperature and reduced pressure over the proper catalyst.[15]



(15)

In the absence of a carrier gas, such as CO_2, the reversible catalytic reaction may lead to disproportionation as described earlier.

The more nearly saturated an alicyclic compound is, the more difficult it is to dehydrogenate. Compounds containing quaternary carbon atoms in the ring, such as compounds with angular methyl groups, are difficult to aromatize. It has been shown[11,13] that compounds containing an angular methyl group do not dehydrogenate or disproportionate at 200°, but at 300° undergo either loss or migration of the methyl group, depending on the preparation of the catalyst.



(11, 13)

II. b. Chemical dehydrogenations

A great variety of chemical agents have been used to bring about dehydrogenation, but due to the lack of space only two may be mentioned. Of general interest and application are sulfur and selenium. The procedure is roughly the same with each; the compound to be dehydrogenated is heated with S or Se in the neighborhood of 300° until the evolution of H_2S or H_2Se ceases, and isolated by various means. There is, again, no general rule of use, the reagent being dictated by the properties of the reactant.

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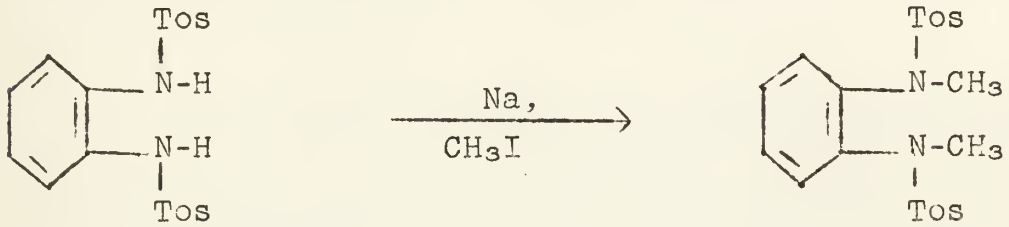
Steric Hindrance Utilized for Ring Formation

Reported by A. Galun October 16, 1953

Most high membered cyclic compounds are prepared by methods which may produce at the same time polymers. The main tool used to suppress the intermolecular reaction is Ruggli's high dilution principle. Recently another principle was applied to achieve the same purpose.

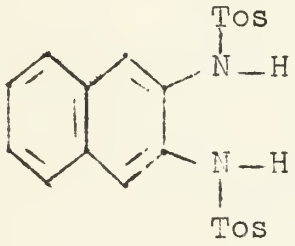
While trying to alkylate N,N' ditosyl-o-phenylene-diamine (I) H. Stetter[1] found that the alkylation of both amino groups is hindered if the alkyl residue exceeds a certain size.

The disodium derivative of N,N' ditosyl-o-phenylene-diamine was reacted with several alkylhalides. It was found that methyliodide gave an 83% yield of N,N'-ditosyl-N,N'-dimethyl-o-phenylene diamine:

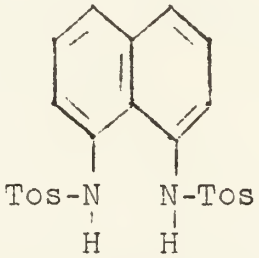


(I)

The corresponding diethyl compound was obtained in only 8.7% and the diallyl in 9.6%. In both cases the mono compounds were the major product. With n-propyl iodide, n-butyl iodide and bromoacetic acid only the mono compounds were formed. Similar results were obtained in case of naphtalene diamines. N,N' ditosyl naphtalene diamine (2,3) (II) yielded 72% of N dimethyl derivative and 13% of the diallyl, but gave only mono substitution with n-propyl and n-butyl halides. An even higher hindrance was encountered in the 1,8 diamine derivatives (III), in which only the monomethyl compound could be prepared.



(II)

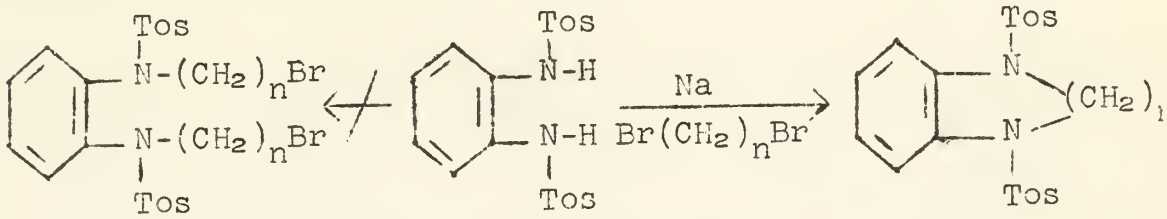


(III)

The author concluded from these results that if alkyl dihalides are reacted with N,N' ditosyl-o-phenylenediamine, only a ring formation could be expected.[2] The other two alternatives of the reaction — the entrance of two alkyl

halides into the molecule or polymer formation — being excluded because of steric hindrance.

The disodium derivative of ditosyl-o-phenylenediamine was reacted with ethylene and propylene dibromides producing 6 and 7 membered rings in 77% and 75% yields respectively:



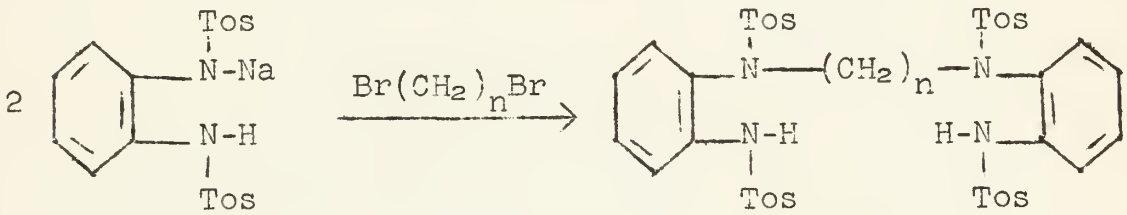
[A ring closure of this type was first carried out by Hinsber and Stupler[4], who reacted N,N' dibenzenesulfonyl-o-phenylenediamine with ethylenedibromide and 1,3 dibromopropane, obtaining 6 and 7 membered rings.]

Even a large excess of dibromide did not yield any other products. For optimal yields a 50% excess of dihalide was used. Dibromobutane and dibromopentane gave a yield of 91% and 61%, respectively.

1,6 Dibromohexane and 1,7 dibromoheptane failed to react It seemed that the introduction of six methylene groups into the molecule is already sterically hindered. According to the author this would correspond to the introduction of two propyl groups which was found to be unaccomplishable. The bulky tosyl groups were therefore replaced by methanesulfonyl groups. N,N' dimethanesulfonyl-o-phenylenediamine reacted with 1,6 dibromohexane giving a 26% yield of the 10 membered ring.

On the other hand, when the tosyl groups were replaced by mesitylsulfonyl groups, the highest obtainable ring was 8 membered, and all yields were lowered.

It was tried whether compound IV could be obtained by reacting one mol of a dibromocompound and two mols of <u>mono</u>-sodium derivative according to:

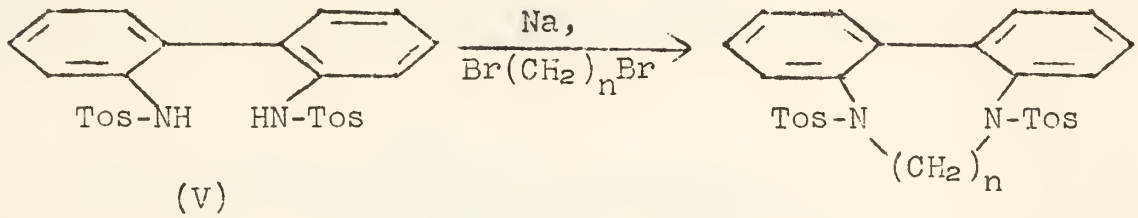


(IV)

In all cases except two only rings were obtained along with unchanged monosodium derivative. With dibromopropane the 9 membered ring was formed in a 34% yield only and 1,6 dibrom hexane gave compound IV as the only product in a 81% yield. Both exceptions were not explained.

The author concludes that ring formation is the preferred reaction, wherever possible at all.

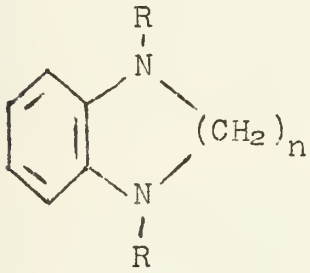
Similar conditions of steric hindrance exist in the ditosyl derivatives of 2,2' diaminodiphenyl (V), which showed preference for ring formation when reacted with dialkyl halides.



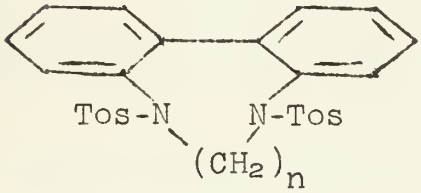
(V)

Yields in this series were lower than in the o-phenylenediamine group.[3] Up to 10 membered rings were prepared, but attempts to obtain a 12 membered ring were unsuccessful (as in case of the o-phenylenediamine derivative). The tosyl group was replaced by the less bulky methanesulfonyl group, but the resultant derivative also failed to react with dibromohexane.

Summary of yields:



R	n	yield %
tosyl	2	77
"	3	75
"	4	91
"	5	61
"	6	0
H_3CSO_2	6	26
$(H_3C)_3C_6H_2SO_2$	4	48
"	5	0



n	yield %
2	42
3	45
4	36
5	30
6	0

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THE ELECTRICAL EFFECT OF THE TRIMETHYLSILYL GROUP

Reported by P. Wiegert October 16, 1953

The first investigation of the trimethylsilyl group's electrical nature when bonded to carbon was carried out with carboxylic acids.[1] Dissociation constants were determined for a number of substituted acetic acids with the following results.

Table I

DISSOCIATION CONSTANTS FOR RCH_2CO_2H at 25°

	R	$K \times 10^5$	$K/K_{(AcOH)}$
I	Me_3Si	0.60	0.34
II	$Me_3SiOSiMe_2$	.60	.34
III	$ØMe_2Si$	.54	.31
IV	Me_3SiCH_2	1.24	.71
V	Me_3C	1.00	.57
VI	Me	1.34	.77
VII	H	1.75	1.00

These data show that the organosilicon substituents in acids I-IV decrease the acid strength, presumably by an inductive effect of electron release to alkyl and hydrogen. Also, acid IV shows that the effect diminishes rapidly in a saturated carbon chain.

Similar effects are observed with substituted benzoic acids.[2] Trimethylsilylbenzoic acids are weaker than benzoic acid, the decrease in acid strength being considerably greater for the meta-isomer than for the para-isomer.

A consideration of the saponification rates of the ethyl trimethylsilylbenzoates also leads to the conclusion that the trimethylsilyl group is slightly electron-donating in the para-position and rather more so in the meta-position.[3]

As would be predicted the trimethylsilyl group increases the basicity of aliphatic amines.[4,5]

Table II

THE POLAR EFFECT OF ORGANOSILICON SUBSTITUENTS IN ALIPHATIC AMINES[5]

Amine #1	Amine #2	Kb #1 / Kb #2
$Me_3SiCH_2NH_2$	$MeNH_2$	1.82
$Me_3Si(CH_2)_2NH_2$	$CH_3CH_2NH_2$	1.73
$Me_3Si(CH_2)_3NH_2$	$CH_3CH_2CH_2NH_2$	1.14

Once again it is apparent that the effect falls off rapidly as the trimethylsilyl group is moved away from the amino group.

These experiments led to the conclusion that the trimethylsilyl group should be an ortho-para director. This question was first directly investigated by Benkeser and Brumfield[6] who used copper nitrate in acetic anhydride to nitrate trimethylphenylsilane. The total yield of 65% was a mixture of ortho-(30%), meta-(40%) and para-(30%) nitro isomers, along with a 24% yield of nitrobenzene as a cleavage product. Nitration of trimethylbenzylsilane gave a total yield of 66% which consisted of 80% of the ortho and 20% of the para-isomer. The cleavage product amounted to only 5% (nitrotoluenes).

These results giving a ratio of 30/40/30 for ortho/meta/para isomers of nitrophenyltrimethylsilane indicate that the trimethylphenylsilyl group is a weak ortho-para director. However, if the nitrobenzene had been formed by cleavage of only the meta nitro isomer, the ratio 30/40/30 would be 22/56/22 and the trimethylsilyl group would have to be considered a meta director.

Accordingly the nitration question was reinvestigated[7] under conditions giving only a small amount of cleavage. Fuming (90%) nitric acid at 0-10° in acetic anhydride reacting with trimethylphenylsilane gave an isomer ration of 26.6/41.7/31.6 and 6.8% of nitrobenzene. If all nitrobenzene is assumed to be meta derived the ratios become 25.5/46.6/30.2 so that Me_3Si- is a weak ortho-para director (The large amount of ortho-isomer is rather surprising since t-butylbenzene gives practically all para- due to steric hindrance.).

In keeping with the idea of Me_3Si being a weak ortho-para director, trimethylphenylsilane is nitrated somewhat easier than benzene as was shown by competitive nitration of a mixture of the two.[7]

Comparison of the electronegativities of silicon and carbon on the Pauling electronegativity scale[8] shows a difference of 0.7 unit, suggesting an electron-releasing tendency for silicon.

These considerations would lead one to believe that the trimethylsilyl group is slightly electron releasing no matter to what moiety it happens to be attached.

However, measurements of certain dipole moments[9] seem to show that the trimethylsilyl group may also act as an electron accepting group if there is some other group present which has strong electron-releasing properties. The suggestion was made that a resonance structure was possible in which the valence shell of silicon expanded to hold ten electrons.

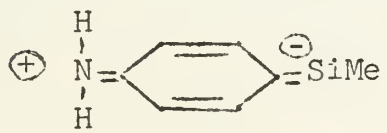

Figure I

This postulate is easily checked for the importance of such resonance may be inferred by a comparison of the base strengths of m- and p-trimethylsilylanilines and -dimethylanilines, and the acid strength of appropriately substituted phenols. If resonance of the type illustrated above is of significance in

the trimethylsilyanilines and -dimethylanilines, then the base strength of the p-amine should be less than that of the unsubstituted amine itself. However, if an electron-releasing effect were of greater importance then the stronger base would be the p-amine rather than the unsubstituted amine. Similarly, the trimethylsilylphenols should be stronger acids than phenol itself due to resonance contributions of the type illustrated in Figure 2.

Figure II

These ideas were checked by Benkeser and Krysiak[10] who determined the apparent acidity constants of substituted dimethylanilinium ions and the apparent ionization constants of certain substituted phenols.

Table III

APPARENT ACIDITY CONSTANTS OF DIMETHYLANILINIUM IONS

Substituent	pKa
H	4.35
p-Me_3Si	3.98
m-Me_3Si	4.41

Table IV

APPARENT IONIZATION CONSTANTS OF PHENOLS

Substituent	pKa
H	10.85
p-Me_3Si	10.64
m-Me_3Si	11.01

The data show that both p-trimethylsilylaniline and -dimethylaniline are weaker bases than aniline and dimethylaniline, respectively. Also p-trimethylsilylphenol is a stronger acid than phenol itself. Just the opposite is true for the meta-isomers because resonance of the type shown in figures I and II is not possible. Therefore the p-trimethylsilyl group tends to release electrons by induction, making anilines stronger bases and phenols weaker acids.

Apparently, however, there are situations in which the silicon atom may not expand its valence shell as shown in figures I and II in spite of the presence of strong electron-releasing functional groups in the para position. Benkeser and Krysiak[11] found the following order for the ease of cleavage of trimethylarylsilanes bearing the substituents indicated.

$$\text{p-MeO and p-Me}_2\text{N} > \text{m-MeO} > \text{m-Me} > \text{H} > \text{p-Cl} > \text{m-Cl} > \text{m-Me}_2\text{N}$$

The ease of cleavage by acidic reagents seems to be governed by the electron density at the aryl C-Si bond. This may be explained by resonance structures of the type shown in figure III, which could then be attacked by a proton at the carbon atom as shown.

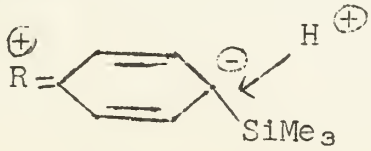

Figure III

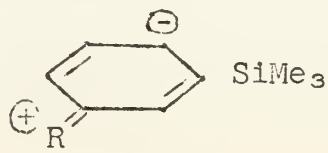

Figure IV

Such ideas also explain why the meta isomers should be more

difficult to cleave (figure IV).

In summary, the trimethylsilyl group may act as either an electron-donating or an electron-accepting function, depending on its environment. When attached to aliphatic acids or amines the group is electron donating; this is also true when it is oriented meta to a hydroxyl or amino group on an aromatic nucleus. However, when the trimethylsilyl group is oriented para to a strong electron-donating group (e.g. hydroxyl or amino) the silicon-containing function becomes an electron acceptor.

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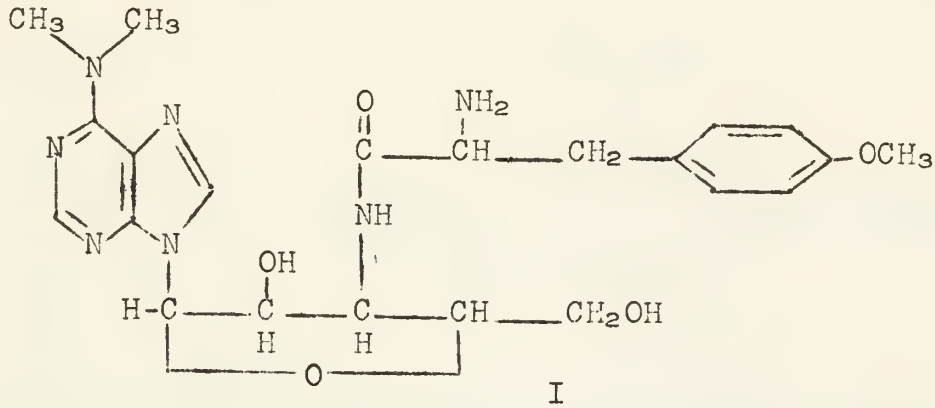
PUROMYCIN

Reported by Richard Fulmer October 23, 1953

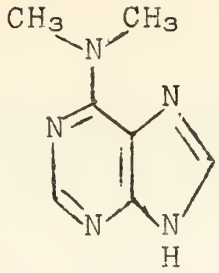
In 1952, Porter and coworkers[1] obtained from soil by the usual dilution methods a mold, Streptomyces albo-niger, so named because it produces white spores and also has the ability to elaborate an olivaceous-black soluble pigment when cultured on certain media. This new mold species is capable of producing a hitherto undescribed antibiotic possessing action against certain bacteria and also some of the protozoan species Trypanosoma, particularly those causing sleeping sickness. This antibiotic is called Puromycin, but is also referred to as Achromycin (an American Cyanamide Company Trademark) because it is devoid of pigment in the crystalline state. Through degradative and synthetic studies[2] the following has been established as the correct structure:



I

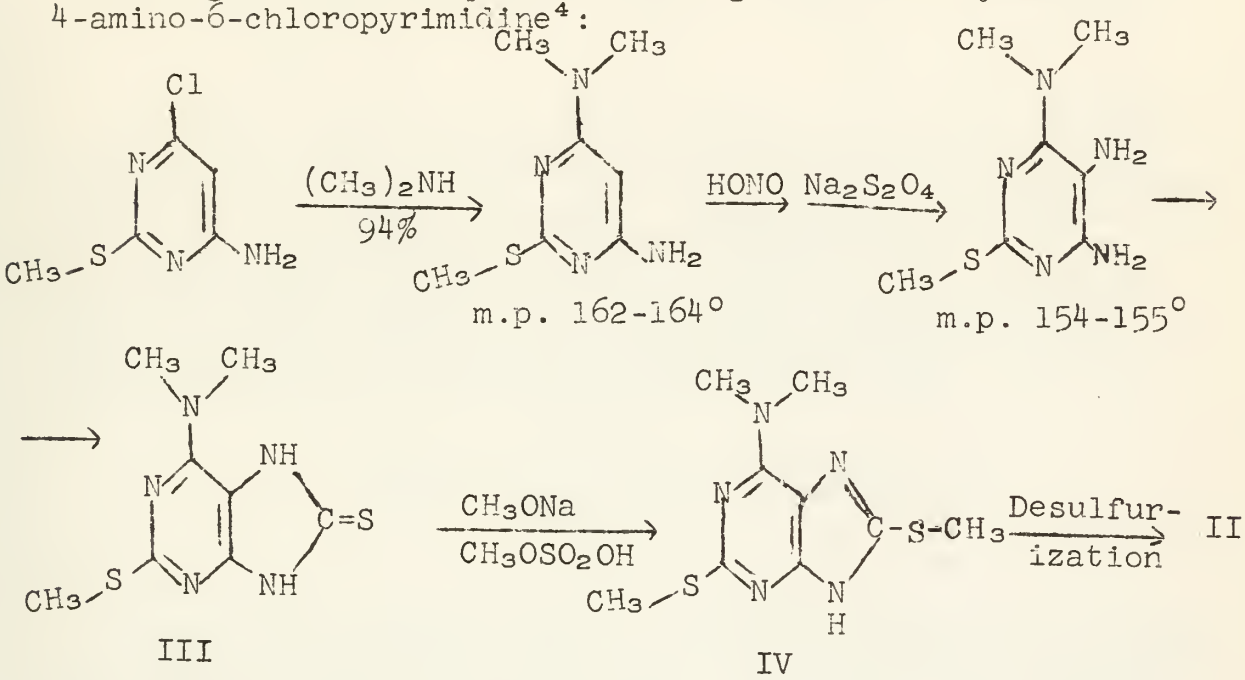
Puromycin, $C_{22}H_{29}N_7O_5$, m.p. 175.5-177°, $[\alpha]_D^{25}$ -11° [ethanol], can be crystallized as the free diacidic base, or as a dihydrochloride or a monosulfate salt. Molecular weight data are in agreement with the empirical formula above. Preliminary analyses showed pKa's at 6.8 and 7.2, the presence of one amino group (Van Slyke), one methoxyl group, two N-methyl groups, and five active hydrogens. The infrared spectrum shows absorption maxima for -OH or -NH and a band slightly displaced to 6.05μ for the carbonyl of the amide function.

The most useful degradative procedure was alcoholysis with ethanolic hydrogen chloride which cleaved puromycin into three fragments. One of these was an amphoteric compound that precipitated from the cleavage mixture as a dihydrochloride, $C_7H_9N_5 \cdot 2HCl$, m.p. 225-227 (dec.), and yielded a free base $C_7H_9N_5$ possessing two N-methyl groups and one active hydrogen. From the molecular formula, a structure containing two rings and four double bonds was indicated. The high nitrogen content, the amphoteric nature of the compound, the ultraviolet maximum at 280 mμ, and the infrared N-H peak at 3.8μ suggested the structure as that of dimethyladenine:



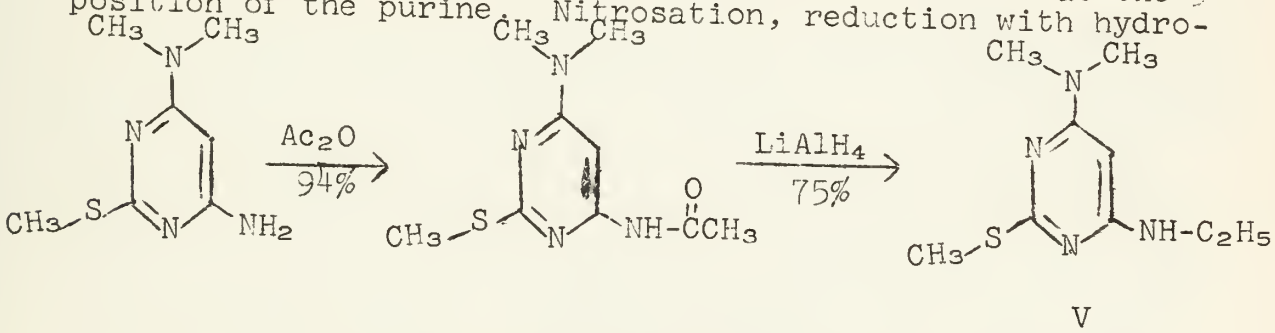
II

This structure was confirmed by comparison with an authentic sample prepared by Baker and coworkers[3] using the following reaction sequence starting with 2-methylmercapto 4-amino-6-chloropyrimidine[4]:



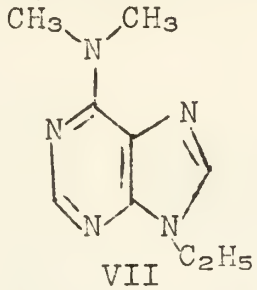
Compound II was also checked with samples prepared by a different route.[5] The cyclization using CS_2 was previously reported by Cook and Smith.[6]

Baker[3] also synthesized the 7- and 9-ethyl derivatives of II as models to demonstrate the position of attachment of the sugar moiety in puromycin. By comparison of their ultraviolet spectra with that of the antibiotic and by other synthetic experiments this linkage was established at the 9-position of the purine. Nitrosation, reduction with hydro-

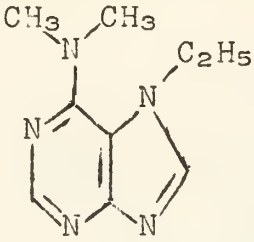


sulfite, ring closure with carbon disulfide, and methylation afforded authentic 2,8-bis-(methylmercapto)-6-dimethylamino-9-ethylpurine (VI). Desulfurization resulted in a 74% yield of 6-dimethylamino-9-ethylpurine (VII). Ethylation of the sodium salt of IV with ethyl iodide gave a readily separable

mixture of 31% of VI, m.p. 131-132°, and 18% of 2,8-bis-(methylmercapto)-6-dimethylamino-7-ethylpurine, m.p. 161-163°. Desulfurization of the latter formed 6-dimethylamino-7-ethylpurine, (VIII), which was isolated as the picrate.

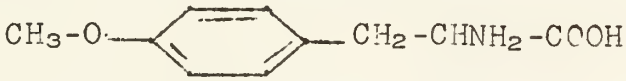


VII



VIII

A second fragment obtained from the ethanolic hydrogen chloride treatment of puromycin was a hydrochloride having the formula $C_{12}H_{17}NO_3 \cdot HCl$. This proved to be the ethyl ester formed in the original cleavage. Permanganate oxidation of the hydrolyzed acid portion yielded anisic acid, and the Van Slyke determination proved the original to be an amino acid. Further analysis, m.p. comparison, spectral and rotation studies, and representative derivatives characterized the acid as L-p-methoxyphenylalanine, (IX).



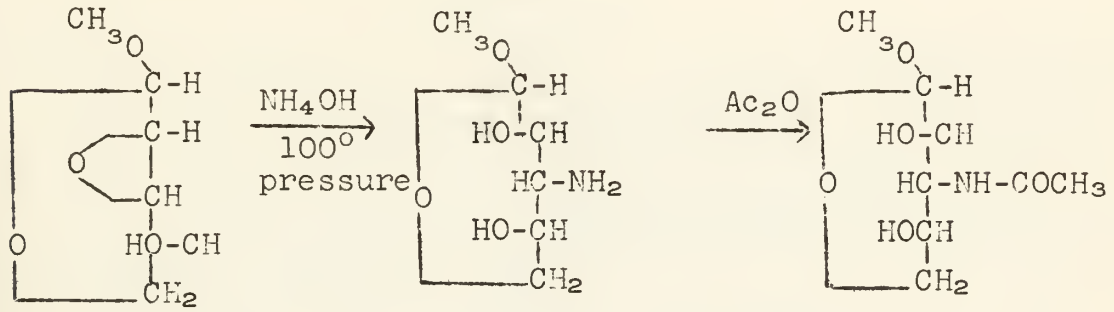
IX

The third fragment from the ethanolic degradation treatment was a hydrochloride melting at 158-158.5° and having the empirical formula $C_5H_{11}NO_4 \cdot HCl$. Characterizing reactions of the free base were a positive Van Slyke, a positive Fehling's test, a positive Brady's reaction, a negative ninhydrin test (2-amino sugars give a positive ninhydrin test), and the formation of furfural on deamination and subsequent treatment with phosphoric acid. The amino sugar consumed 3.8 moles of periodic acid in three hours while the N-acetyl derivative reacted with only 2 moles in the same length of time.

The absence of a carbonyl band in the infrared spectrum of this amino sugar and the above data permit postulation of this portion as a hemiacetal form of a 3- or 4-aminopentose. The formation of a triacetate of puromycin and its subsequent partial deacetylation with alcoholic ammonia to N-acetylpuromycin assign to the compound two free alcoholic groups. N-Acetylpuromycin failed to react with periodic acid, thus requiring the free amino group of I to be in the amino acid portion and this also eliminated a 4-aminopentose structure for the amino sugar. A negative Brady's test until after hydrolysis indicated a glycosidic linkage in puromycin.

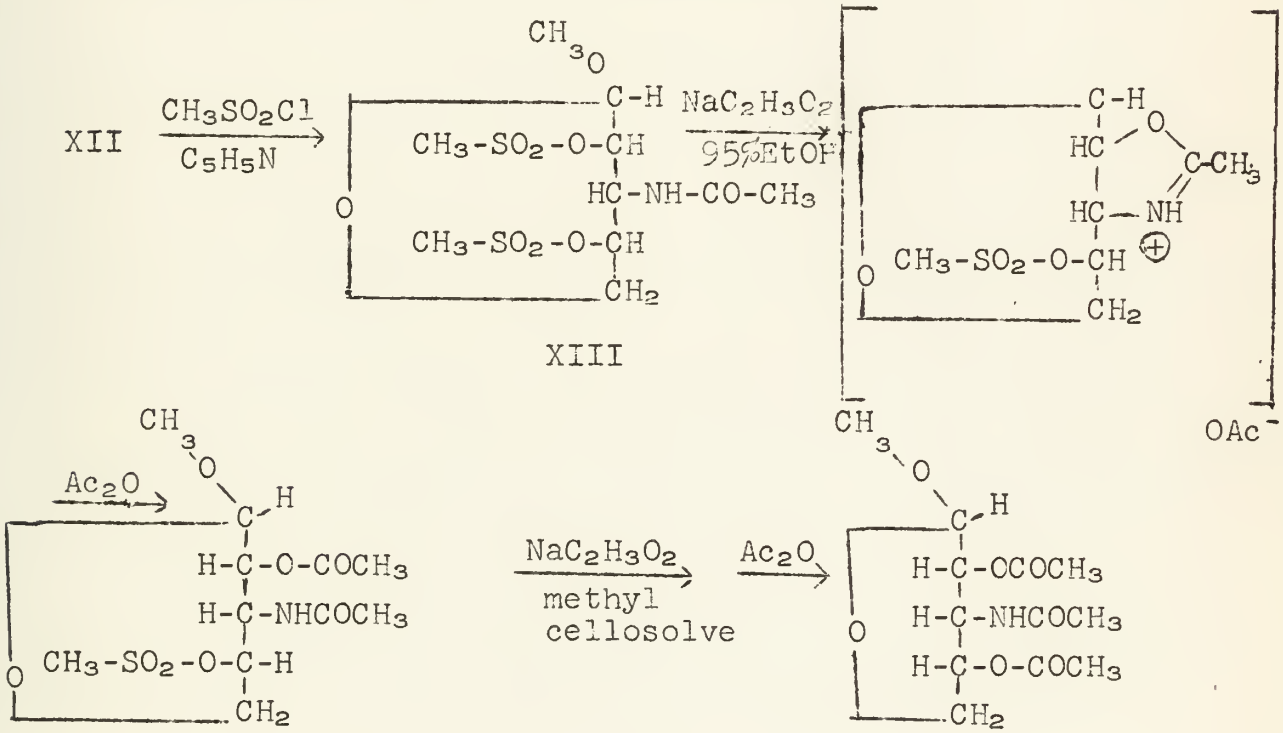
It is interesting that this is the first known 3-amino sugar and the first known aminopentose to exist in a natural source. A neat conversion which immediately allowed the elimination of two of the four possible pentose configurations

from consideration was catalytic hydrogenation to an amino-alcohol possessing no optical activity, therefore meso. This automatically limited the parent sugar to a ribose or xylose. The structure has now been proved to be 3-amino-D-ribose by synthesis from L-arabinose via β-methyl 2,3-anhydro-L-ribopyranoside (X) by Baker.[7]



X XI XII

Since the N-acetyl derivative of β-methyl-3-amino-L-xylopyranoside (XII) failed to consume periodate, the alternate structure, β-methyl-2-amino-L-xylopyranoside, which could be formed on ring opening of X, was eliminated. It should be noted that a trans configuration of amine and hydroxyl is obtained by Walden inversion.



Reaction of XIII, β-methyl-2,4-dimesyl-3-acetamino-L-xylopyranoside, with sodium acetate in ethanol caused elimination of one mesyl group with inversion via an oxazoline. Although this is the first known example of this reaction in the carbohydrate field, the reaction has been described with trans-acetaminocyclohexanol-2-tosylate.[8] Further treatment gave the triacetyl derivative. Direct treatment of XIII with sodium acetate in 95% methyl cellosolve caused

elimination of both mesyl groups with inversion to an all cis-configuration. Hydrolysis with boiling 1% hydrochloric acid gave 3-amino-D-ribose hydrochloride which was shown to be identical with the amino sugar obtained from puromycin.

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ELIMINATION REACTIONS OF ESTERS

Reported by Allan S. Hay October 23, 1953

Linstead et al[1(a,b,c)] have made a general survey of the reaction which involves elimination of an acyl group β to a carbethoxy group to give α,β-unsaturated products, or products derived therefrom in which the α,β-unsaturated compound is an intermediate. The reaction can be represented by the following scheme:

$$YOCRR'-CHR''X + OH^- \rightarrow RR'C=CR''X + YO^- + H_2O$$

where X is an electron-attracting group such as carbethoxyl, and Y is an acyl group.

Isolated examples of analogous reactions can be found in the literature. The formation of α,β-unsaturated products from the corresponding β-halides is related to this reaction. One of the earliest examples was the conversion of β-acetoxyhydrocinnamic acid to cinnamic acid by heating with excess barium hydroxide or by heating the acid alone above 200°C[2].

$$\emptyset CH(OAc)-CH_2-COOH \rightarrow \emptyset CH=CH-COOH$$

Schmidt and Rutz[3] converted various β-acetoxynitro-compounds (I) to the corresponding nitro-olefins (II) by the action of calcium carbonate in refluxing ether solution.

$$\underset{\text{I}}{RCH(OAc)-CH_2NO_2} \rightarrow \underset{\text{II}}{RCH=CHNO_2}$$

When the reaction was applied to carbohydrate chemistry, Fischer and Sowden[4] found that only the β-acetoxy-group was eliminated.

$$AcOCH_2-[CHOAc]_4-CH_2NO_2 \rightarrow AcOCH_2-[CHOAc]_3-CH=CHNO_2$$

Vinylacetylenes have been prepared by Eglinton and Whiting[5] by the action of base on the p-toluenesulfonates of β-acetylenic alcohols.

$$RCH(OTs)-CH_2-C\equiv CH \rightarrow R-CH=CH-C\equiv CH$$

The formation of unsaturated compounds by the isomerization of certain lactones is also a related process and has been studied in detail by Linstead and co-workers.

In order to confirm that these reactions involve the elimination of an acyl group, ethyl β-hydroxy butyrate was subjected to conditions which convert the β-acetoxy derivative to a mixture of crotonic and β-hydroxy butyric acids. No dehydration occurred, and even higher concentrations of alkali had no effect.

A large number of esters were subjected to alkaline hydrolysis. Three structural features of the molecule were

modified. The electron-attracting groups, X, used were ester and carboxylic acid; the carbon skeletons used were butyric, β-phenylpropionic, β-phenylpropionic, and cyclohexylacetic; and the acyl groups, Y, were acetyl, benzoyl, methanesulfonyl, p-toluene sulfonyl, nitro-, phosphonyl, and diphenylphosphonyl.

There are two competing reactions, elimination and hydrolysis. It was found that the proportion of elimination to hydrolysis increased with the strength of the acid YOH. When the resulting acid is conjugated with a benzene ring, for example, as in cinnamic acid, the proportion of elimination to hydrolysis is also greater. When the phenyl group is in a more remote position it has no appreciable effect.

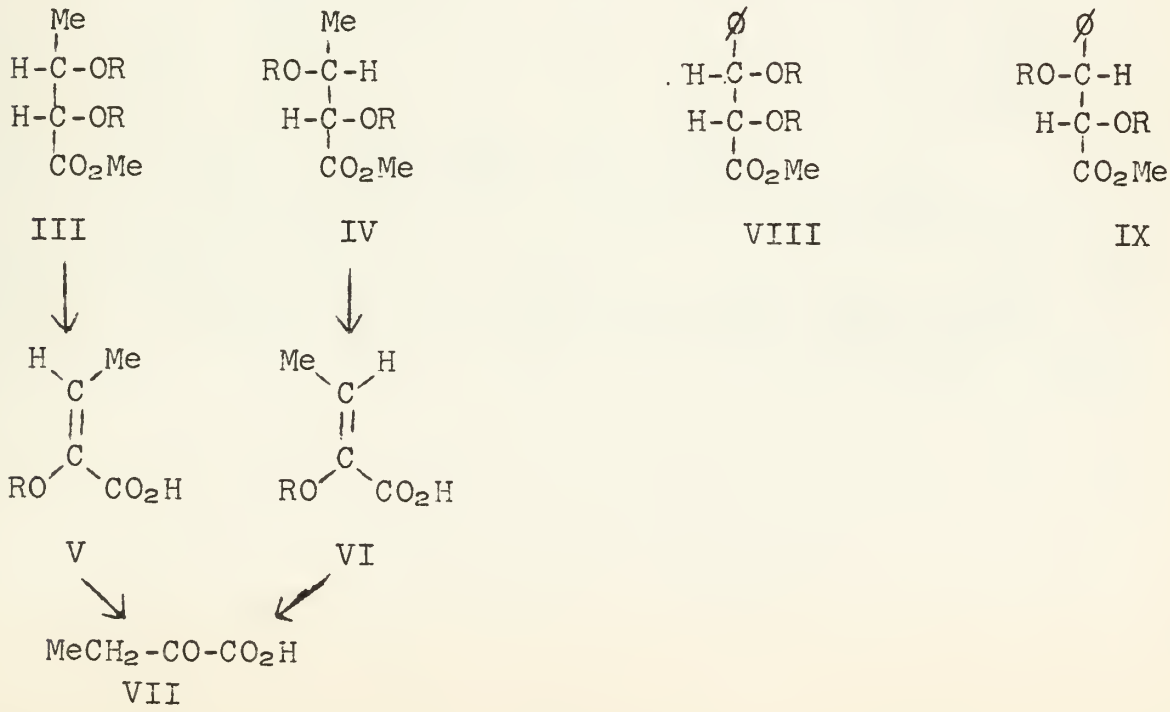
Treatment of ethyl 1-acetoxycyclohexyl acetate with alkali gave 25% acyl elimination and the elimination product was exclusively the α,β-acid. By contrast, dehydration of hydroxycyclohexylacetic acid under acidic conditions normally yields predominantly β,γ-unsaturated material.

The reaction was further extended to derivatives of α,β-dihydroxy acids. Elimination would be expected to occur preferentially at the β-position and thus yield α-keto acids by way of the corresponding enols.

$$>C(OR)-CH(OR)-CO_2Et \rightarrow >C=C(OR)-CO_2H \rightarrow$$

$$>C=C(OH)-CO_2H \rightarrow >CH-CO-CO_2H$$

Experimentally, the reaction was run on a number of di-p-toluene sulfonates, diacetates, and dibenzoates. The disulfonate was found, in every case, to yield the corresponding α-keto acid but the diacetates and dibenzoates were generally hydrolyzed to the respective dihydroxy-compounds. For example, hydrolysis of the diacetate of methyl erythro-α,β-dihydroxybutyrate (III, R=Ac) with concentrated aqueous alkali gave only the erythro-dihydroxy-acid.



The four disulfonates (III, IV, R=Ts) all gave α-ketobutyric acid (VII) on hydrolysis. The reaction could be stopped at an intermediate stage by using cold, dilute alkali. Each disulfonate then gave a different, crystalline monosulfonate (V, VI, R=Ts) which proved that the monosulfonates were α-substituted crotonic acids and confirms the expected preferential elimination of the β-substituent. Assuming that trans-elimination occurred, the cis- and trans-configurations may be given to (V) and (VI), respectively. From the four disulfonates of α,β-dihydroxy-β-phenylpropionate (VIII, IX; R=Ts) under the same conditions only one unsaturated monosulfonate was obtained which on further hydrolysis gave phenylpyruvic acid.

Treatment of a compound containing two tosyl-groups on vicinal carbons with sodium iodide results in the formation of the corresponding olefin[6] if one of the tosyl groups is primary, whereas if both groups are secondary they are usually resistant to such treatment[7]. It is interesting to note that treatment of the dimethane sulfonates (III, IV, VIII, IX; R=Ms) with sodium iodide in acetone gave methyl cis-crotonate, methyl trans-crotonate, methyl cis-cinnamate, and methyl trans-cinnamate, respectively. That is, the erythro- and threo- esters gave cis- and trans- products, respectively, the overall result being one of cis-elimination. This is opposite to the result obtained when dibromides are debrominated with potassium iodide. The reaction is being studied in more detail to confirm its generality.

In applying the reaction to derivatives of dibasic polyhydroxy acids the stereochemical results of these reactions can be explained by a mechanism of trans-elimination in all cases.

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Synthesis of Macrocyclic Compounds

Reported by Leroy Whitaker October 23, 1953

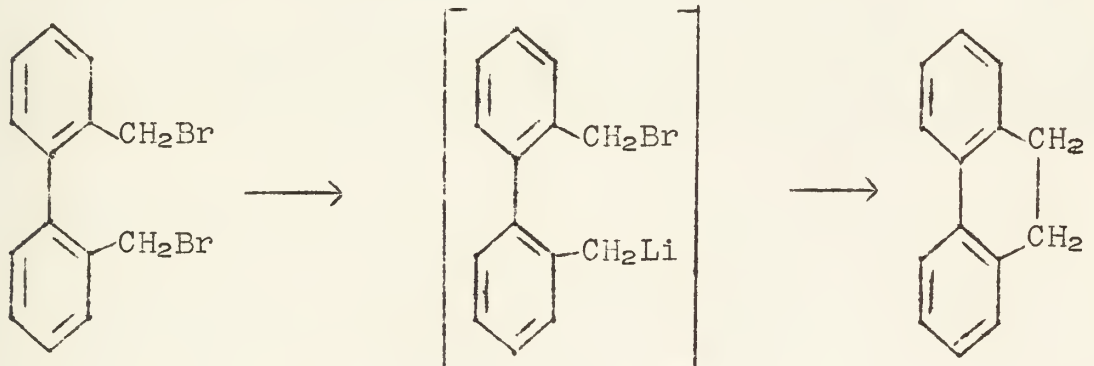
In 1941 Wittig and Witt[1] found that the reaction of benzyl bromide with phenyllithium led not to the expected diphenyl methane, but instead to dibenzyl and bromobenzene. They postulated that the bromine and lithium exchanged places to form bromobenzene and benzyllithium, which reacts with more benzyl bromide to form dibenzyl.

$$C_6H_5CH_2Br + C_6H_5Li \rightarrow C_6H_5Br + C_6H_5CH_2Li$$

$$C_6H_5CH_2Li + C_6H_5CH_2Br \rightarrow C_6H_5CH_2CH_2C_6H_5$$

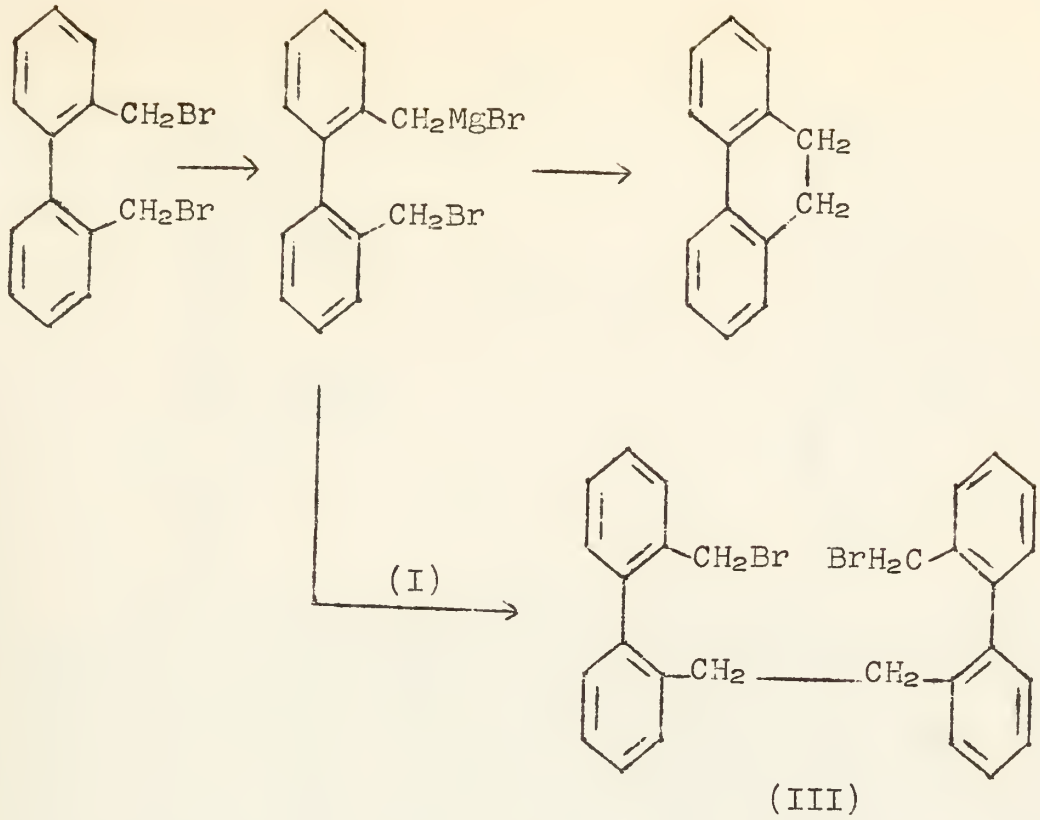
The presence of the intermediate benzyllithium is indicated by the characteristic lemon-yellow color, which quickly vanishes as the benzyllithium reacts with the benzyl bromide.

Phenyllithium causes the intramolecular cyclization of 2,2'-bis-(bromomethyl)biphenyl (I) to form dihydrophenanthrene (II).[2] This reaction is believed to proceed by a mechanism similar to the one above. The lithium in the intermediate evidently attracts preferentially the bromine atom in the same molecule.[3]

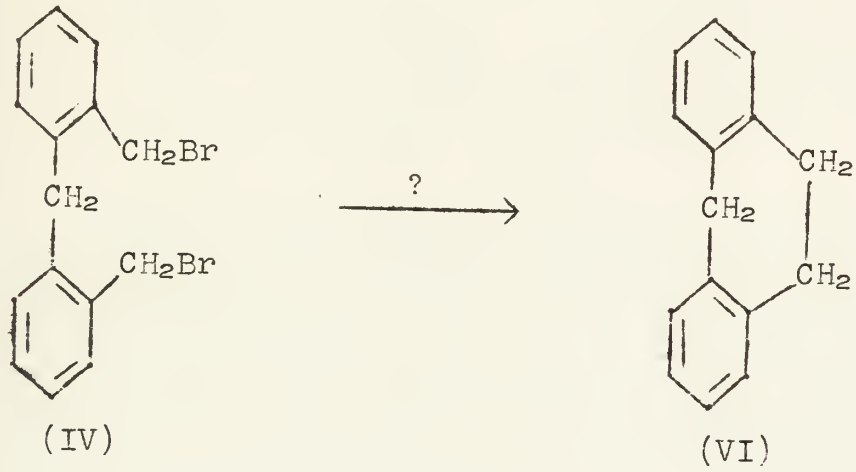


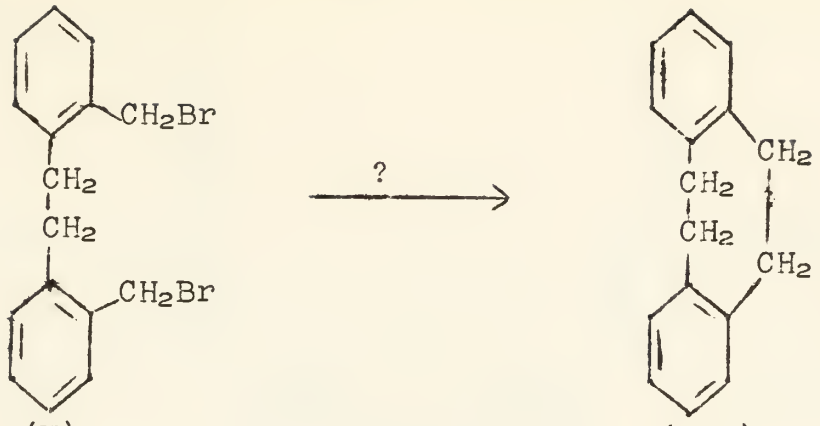
(I) (II)

When attempts were made to prepare a Grignard reagent from (I) a 40% yield of (II) was isolated.[4] In addition to (II) some 1,2-di-(2'-bromomethyl-2-diphenyl)ethane (III) and more complex products were obtained. The following scheme suggests a possible mechanism.



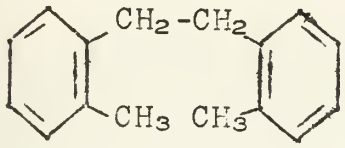
The question arose whether phenyllithium would react with 2,2'-bis-(bromomethyl)-diphenylmethane (IV) or 2,2'-bis-(bromomethyl)-dibenzyl (V) in a manner analogous to the reaction with (I), thereby permitting the synthesis of seven- and eitht-membered ring systems, such as 1,2,4,5-dibenzocyclohepta-1,4-diene (VI) and 1,2,5,6-dibenzocycloocta-1,5-diene (VII).



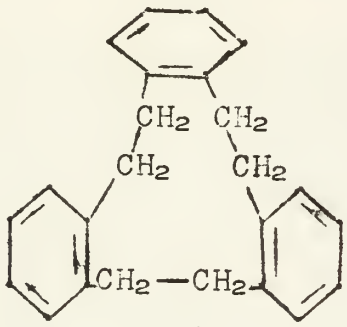


(V) (VII)

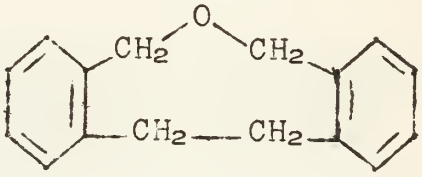
The synthesis of (VII)from (V) would be analogous to the reaction of o-xylylene dibromide with metallic sodium.[5] In addition to 6% of (VII), o-xylylene dibromide and sodium in refluxing dioxane yield lesser amounts of 1,2-di-o-tolylethane (VIII) and s-tribenzocyclododecatriene (IX). In ether and ethyl acetate, o-xylylene dibromide and sodium yield 5% of o-xylene, 6% of (VIII), and lesser amounts of (IX) and a compound believed to be 3,4,7,8-dibenzooxacyclo-$\Delta^{3,7}$-nonadiene (X).



(VIII)

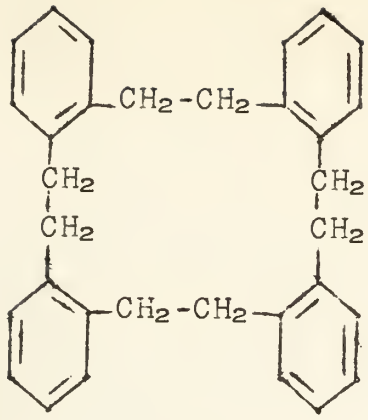


(IX)

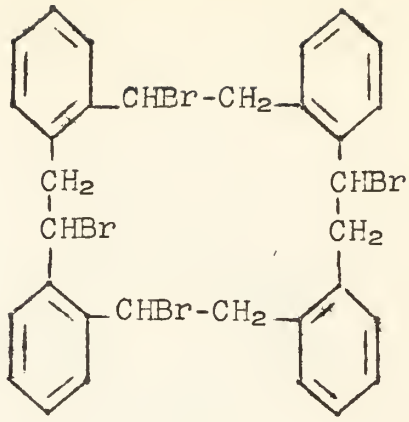


(X)

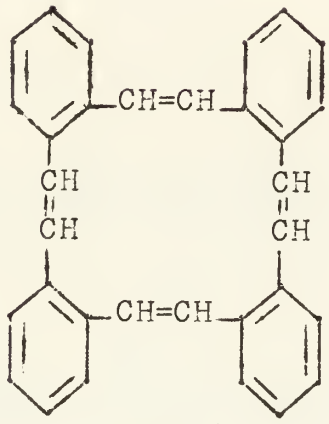
When (V) was treated with phenyllithium, two products were obtained:[3] a halogen free polymer and a crystalline hydrocarbon $C_{32}H_{32}$. The yield of the two products was 60% and 40% respectively. For the crystalline hydrocarbon the structure of 1,2,5,6,9, 10,13,14-tetrabenzocyclohexadeca-1,5, 9,13-tetraene (XI) is indicated by the synthesis. It is confirmed by the formation of a tetrabromo derivative (XII) by means of N-bromosuccinimide and by the dehydrobromination of (XII) by means of dimethylaniline to 1,2,5,6,9,10,13,14-tetrabenzocyclohexadeca-1,3,5,7,9,11,13,15-octaene (XIII). The infrared spectrum of (XIII) indicates the presence of four double bonds. In addition, the spectrum shows that the four stilbene double bonds have <u>trans</u>-configuration.



(XI)

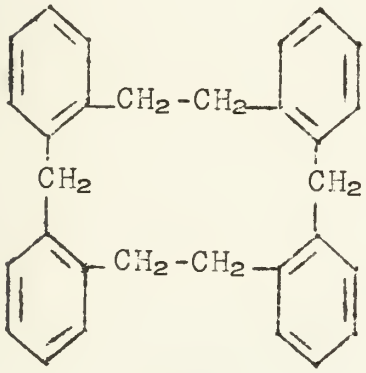


(XII)

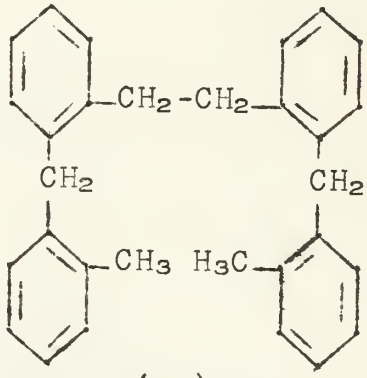


(XIII)

Analogous results have been obtained in experiments with (IV).[5] The reaction of (IV) with phenyllithium gave a yield of 60% of a crystalline hydrocarbon $C_{30}H_{28}$, for which by analogy the formula of 1,2,4,5,8,9,11,12-tetrabenzocyclotetradeca-1,4,8,11-tetraene (XIV) is suggested. It is not impossible that "dimerization" took place only on one side of the molecule while on the other the bromomethyl groups were simply reduced to methyl groups, so that 2,2'-di-(o-methylbenzyl)-dibenzyl, $C_{30}H_{30}$ (XV) was formed; its analysis would be indistinguishable from (XIV).



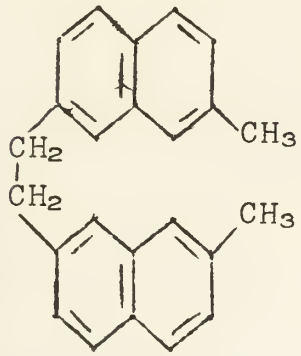
(XIV)



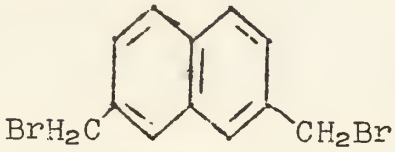
(XV)

Baker and coworkers[6] found that 1,2-di-(7-methyl-2-naphthyl)-ethane (XVI) can be made the main product from the reaction of 2,7-bis-(bromomethyl)-naphthalene (XVII) with metallic sodium in dioxane. The formation of (XV) from (IV) above would be analogous to this reaction. However, Baker and coworkers reported that the reaction of (XVII) with

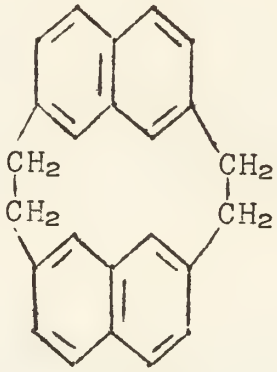
phenyllithium failed, under the same conditions, to yield (XVI) and gave in 20% yield di-(naphthalene-2,7-di-methylene) (XVIII). This is analogous to the formation of (XIV) from (IV) above.



(XVI)

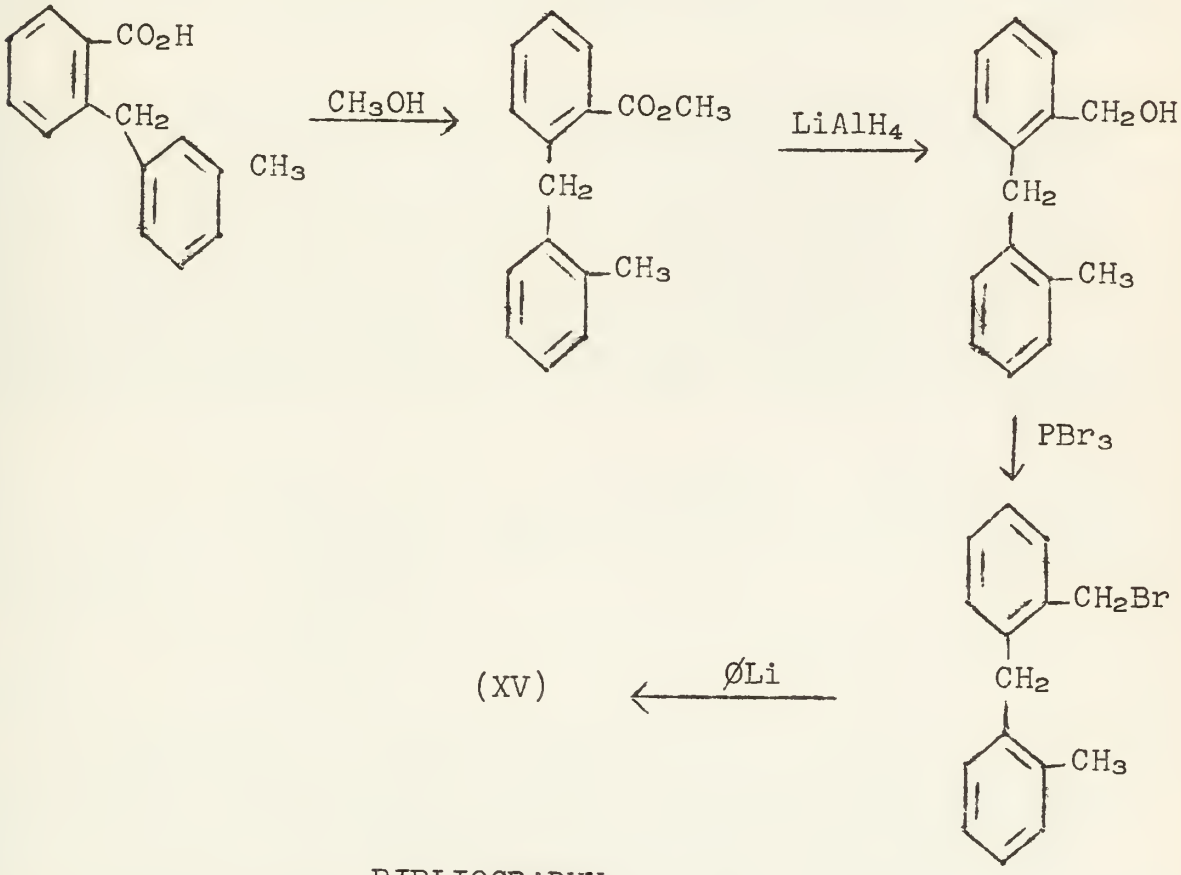


(XVII)



(XVIII)

The hydrocarbon (XV) was synthesized starting with 2-(o-methylbenzyl)-benzoic acid and proved different from (XIV).[3] The steps of the synthesis are shown below.



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THE STRUCTURE OF NITRENES

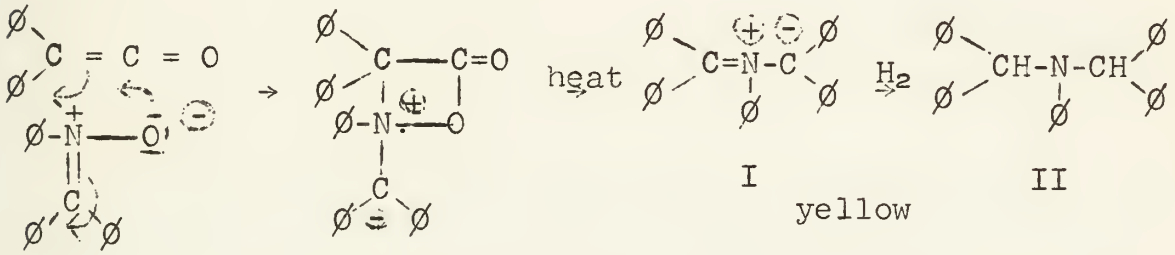
Reported by Joanne G. Arnheim October 30, 1953

The study of the interaction of diphenylketene with nitrones-the N-ethers of oximes- demonstrated that N-phenyl nitrones give addition compounds which, when heated, lose CO_2, and form a novel type of product, called "nitrenes". Staudinger first discovered the nitrenes in 1917 when he reported the preparation of pentaphenyl nitrene.[1] Two years later,[2] he reported on the structure of these compounds and their properties.

Structure Proposed by Staudinger

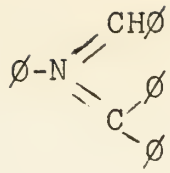
It was noted[2] that the nitrenes produced in these reactions were colored compounds, but less colored than the corresponding nitrones from which they were produced. Reduction of pentaphenyl nitrene (tetraphenyl-N-phenyl nitrene) (I), resulted in a product which failed to give a nitroso derivative and so could not be a secondary amine. This reduction product was found to be identical with dibenzhydrylaniline (II) which was synthesized by another route, although no data for the synthesisis was given in Staudinger's work.

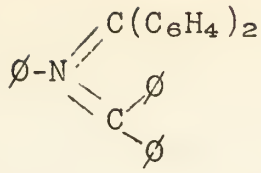
Since a tertiary instead of a secondary amine was the product of the above reaction, Staudinger deduced that a new carbon-to-nitrogen bond must have been formed. He assumed that the primary attack of the ketene must be such that a carbon to oxygen bond was formed, since the nitrene is produced only after CO_2 is lost from a primary addition product. The following reaction sequence was therefore proposed as taking place in the reaction between diphenylketene and diphenyl-N-phenyl nitrone. (Staudinger's formulae which contained pentacovalent nitrogen have been rewritten in modern terms.)

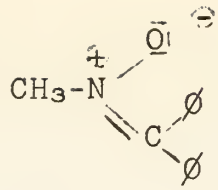


On the basis of this structure, which possesses resonance stabilization, Staudinger was able to explain many reactions of nitrenes. An alternative structure, a cyclic ethyleneimine structure, he discarded because these compounds were known to be colorless and upon reduction to cleave and produce secondary amines. He did state, however, that the ethyleneimine might be in tautomeric equilibrium with the nitrene in certain cases.

A number of other nitrenes were then prepared by Staudinger and their properties studied. They include triphenyl-N-phenyl nitrene (III) and, in impure form, the extraordinarily labile diphenylene-diphenyl-N-phenyl nitrene (IV).







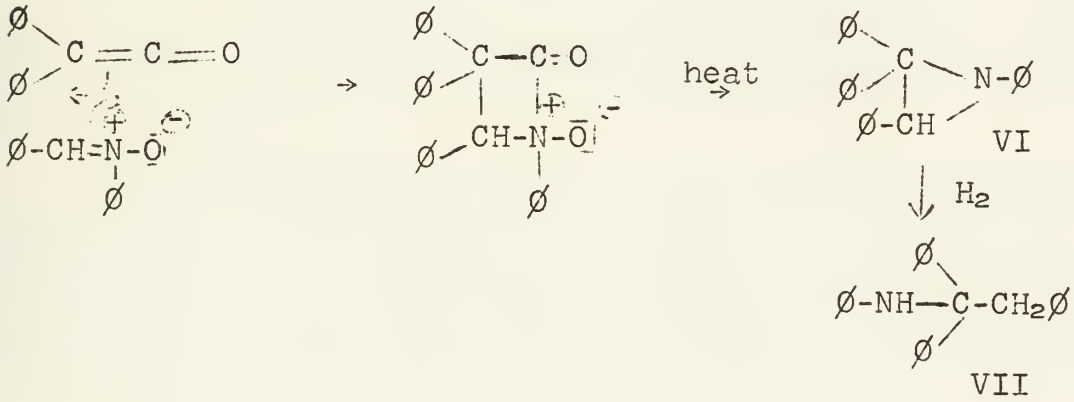
III - pale yellow IV - green V

An attempted synthesis of a nitrene by the reaction of diphenyl-N-methyl nitrone (V) with diphenylketene failed.

Structure Proposed by Taylor, Owen and Whittaker

Objections were soon to be raised, however, to Staudinger's formulation for the nitrenes. Taylor, Owen and Whittaker[3] undertook a reexamination of Staudinger's data primarily because they and others[4] were disturbed by the idea of a pentacovalent nitrogen, which they assumed was implied in the nitrene formula. Although this objection may be met by rewriting the formulae as shown above, these workers were able to disprove Staudinger's structure on an experimental basis Triphenyl-N-phenyl nitrene (III) was prepared[3] and found tobe a colorless compound when pure. It was easily reduced to an amine which must have been a secondary amine because its nitroso derivative was obtained and analysed.

They proposed that the reaction proceeds according to the following sequence:



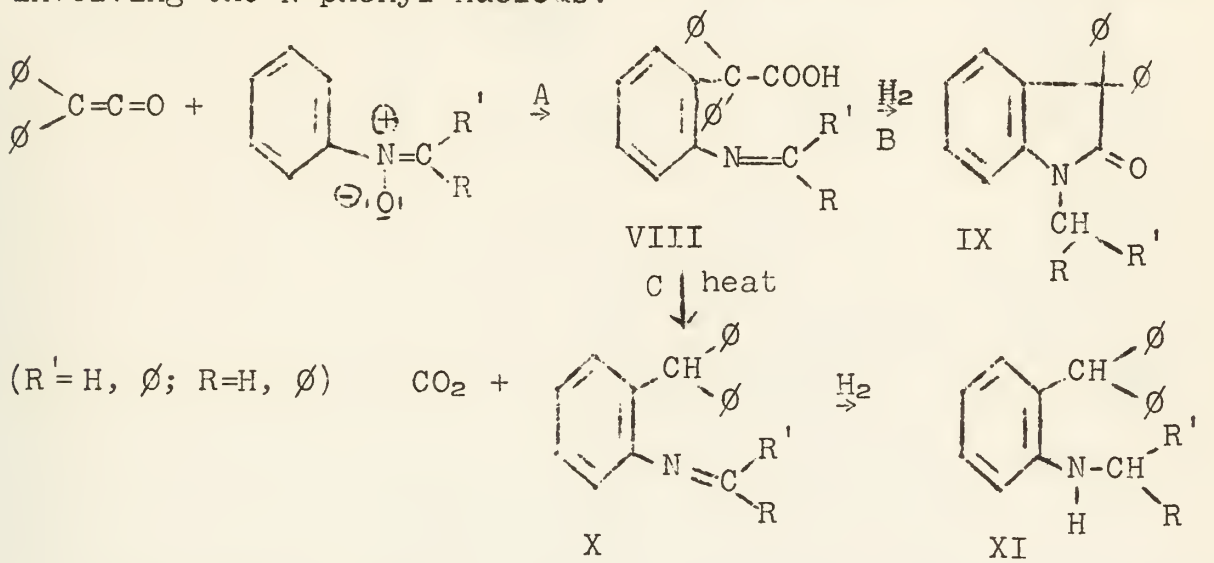
Thus, nitrenes are formulated as ethylene imines. It would have been best had this hypothesis been verified by an independent synthesis of the ethyleneimine (VI), but all attempts to do this proved to be unsuccessful.

A review article written at this time[5] summarized the problem in the following way - "The question as to the structure of the nitrenes must, therefore, be regarded as still unsettled, although the most recent evidence, ... makes it probable that these structures are, in reality, cyclic compounds."

Structure Proposed by Hasall and Lippman

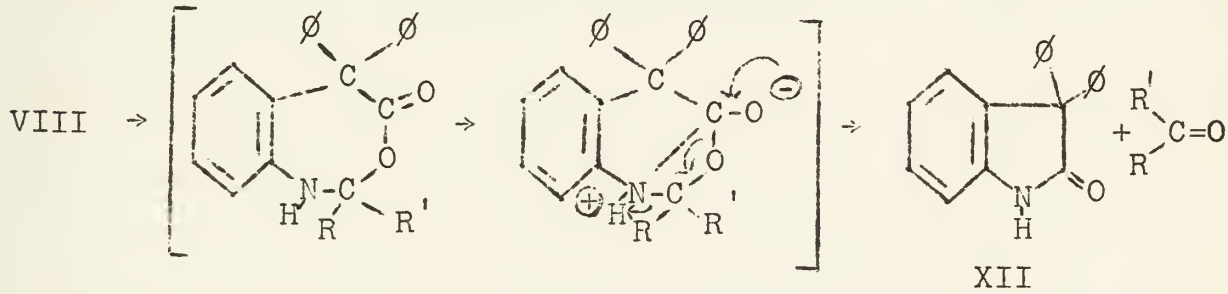
Hasall and Lippman agree[6] also that the structure of nitrenes may best be represented by a cyclic formula, but their evidence has led them to adopt a different type of

formula from (VI). When they attempted the hydrogenation of triphenyl-N-phenyl nitrene with aluminum amalgam, instead of obtaining one product, they obtained three. One of them was identical with compound (VII), but the other two were different from any of the reduction products possible (1-anilino-1,2,2-triphenylethane and 1-anilino-1,1,2-triphenylethane). And, since, when aliphatic radicals or hydrogen replace the aromatic radical in the N-phenyl nitrones, nitrene formation does not take place, the authors suggest a reaction involving the N-phenyl nucleus.



The addition product (VIII), a precurser of the nitrene, was found to absorb one mole of hydrogen, producing a substance (IX), similar to 3,3-diphenyloxindole. This reduction is quite similar to that of the o-nitrophenylacetic acids to give oxindoles.[7]

Further evidence to support this series of reactions was provided by the isolation of 3,3-diphenyloxindole from the mother liquor after formation of the addition product. Staudinger had also obtained a product, at this point, which he could not identify positively. The formation of this product may now be explained either as an ionic chain reaction initiated by water or in the following manner:

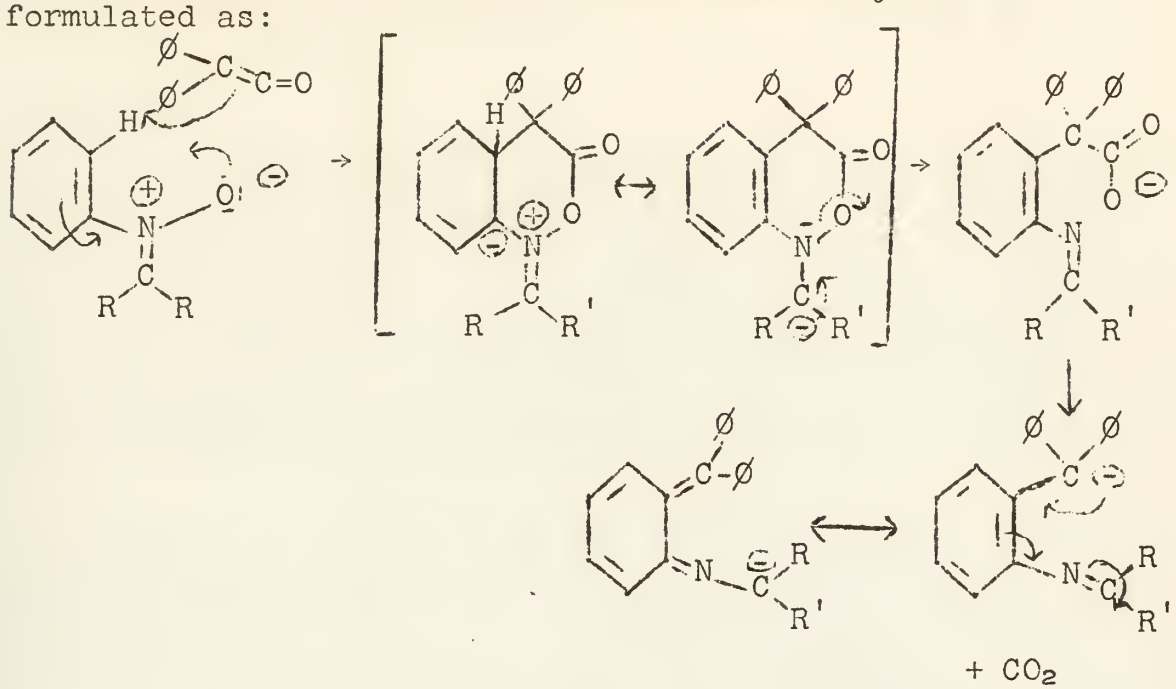


This type of decomposition is not unknown. Rather, it is analogous to the hydrolysis of derivatives of benzylidene anthranilic acid[8] and of benzylidene glycine[9].

Compounds (IX), (XI), (XII) were all prepared by independent routes for comparison with the products obtained. Although the nitrene, itself, has never been prepared by an alternative route, triphenyl-N-phenyl nitrene (X, where R=Ø,

R'=H) was hydrolysed with sulfuric acid to give benzaldehyde and o-aminophenyldiphenylmethane.

The course of reactions A and C above may now be formulated as:



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PHOTOPEROXIDATION INVOLVING SOME TRANSANNULAR PEROXIDES

Reported by Melvin J. Gortatowski October 30, 1953

Introduction

Transannular peroxides are compounds containing a peroxide bridge across the 1,4-positions of a six membered ring (1). The first transannular peroxide discovered is one that, oddly enough, occurs in nature, namely, ascaridol* which is the active principle of chenopodium oil, a powerful anthelmintic. The unusual structure of this naturally occurring transannular peroxide has placed it in a class all its own until about twenty-five years after its discovery, when other peroxides of similar constitution were discovered in connection with intensified studies on sterols and their relation to vitamin D.

The occurrence of such cyclic peroxides is by no means restricted to the alicyclic series. It was noticed that certain polynuclear hydrocarbons such as naphthacene and rubrene lost their fluorescence and color on exposure to sunlight with simultaneous deposition of a crystalline peroxide. It has been shown that the stable "rubrene peroxide" was actually the transannular peroxide of 5,6,11,12-tetraphenylnaphthacene, the peroxide bridge occurring between C_5 and C_{11}.

The fact that light is absolutely necessary for the formation of these transannular peroxides was well illustrated by Dufraisse[2]. A benzene solution of rubrene was kept under oxygen for seven and one-half years with complete exclusion of light and in the presence of many different catalysts, but no peroxide was formed. Under the influence of light, the reaction is complete in a matter of minutes. He found the same to be true in the case of anthracene.

It is with anthracene and its derivatives, together with some alicyclic-type compounds (terpenes and sterols), that this report is concerned in the treatment of the phenomenon of photoperoxidation.

Photoperoxidation in the Aromatic (Anthracene) System

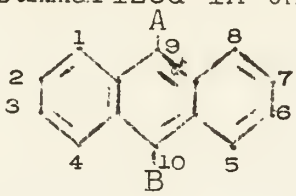
The ability of some polynuclear hydrocarbons like naphthacene and rubrene to undergo the addition of a molecule of oxygen is associated with the reactivity of the meso-positions. Similar meso-positions are found in the anthracene nucleus (9,10-positions). Despite the fact that extensive studies were made on the photochemistry of anthracene in relation to dimer formation, the interesting property of photoperoxidation of anthracene had gone unnoticed until Dufraisse[3] found that exposure of a dilute solution of anthracene in carbon disulfide to sunlight rapidly absorbed oxygen, and a crystalline peroxide was deposited.

* Ascaridol is presently produced on a commercial basis in Germany by photo-oxidation of the corresponding diene[26].

Since it was believed that the reactivity of the meso-positions is a determining factor in ability of a compound to undergo photoperoxidation, studies have been made on varying the groups attached to the meso, as well as nearby positions, in the anthracene nucleus.

The method of study involved a manometric technique[3] to determine the amount of oxygen liberated on thermal decomposition. Structure determination of the peroxides was, in general, carried out by hydrogenation to the known corresponding dihydroxy compound.

Some of the more illustrative examples of effect of groups on the susceptibility toward photoperoxidation and stability of the peroxide are summarized in the table below:



Nature of Group	Type of Peroxide Isolated	Dissoc. Temp.	Chief Products formed on Dissoc.*	Reference
I A=B=H	9,10	120° (explodes)	----	3 and 7
II A=B=ONa	None	----	----	5
III A=B=CCH_3	9,10	180°	Anthraquinone + trace O_2	5
IV A=B=C_6H_5	9,10	180°	O_2(95%) + IV	4
V A=C_6H_5,B=2-Thienyl	9,10	145-150°	O_2(96%) + V	8
VI A=B=2-Thienyl	Resin	----	----	8
VII A=C_6H_5,B=CH_3	(9,10-)	170°	O_2(20%)	7
VIII A=C_6H_5,B=C_2H_5	(9,10-)	200°	O_2(34%)	7
IX A=B=$OCOCH_3$	None	----	----	3
X A=B=C_6H_5C=NH	9,10-	120°	O_2(25%)+CO_2	9
XI A=C_6H_5,B=CN	Resin	----	----	9
XII A=B=CN	None	----	----	9
XIII A=B=Cl	----	----	Anthraquinone	9
XIV A=B=Br	----	----	Anthraquinone	9
XV A=NO_2,B=H	Resin	----	----	6

* Per cent oxygen is based on theoretical amount.

It is possible to conclude that a negative group (CN,COOH, COOEt,$CONH_2$,Cl,Br,NO_2) in the meso (9,10-position) inhibits the formation of a stable peroxide (9 and 6) whereas an electron releasing group tends to enhance formation of a stable peroxide. The most favorable arrangement is found in the cases where both meso-positions hold an aromatic group such as phenyl or 2-thienyl.* It is believed that any group capable of donating electrons through resonance to the meso-position favors peroxide formation.

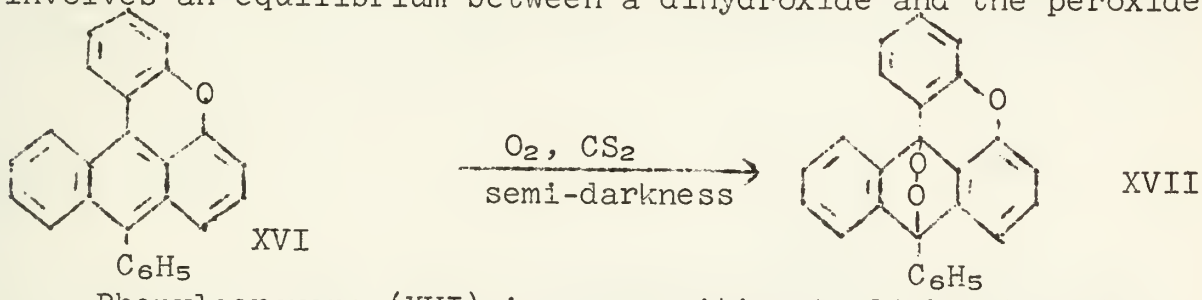
* If both groups are 2-thienyl, an unstable peroxide results (see table above).

The influence of groups located in various positions in the 9,10-dipheny-anthracene nucleus on the photoperoxidizability was studied by Dufraisse and others[10,11,12,13]. In general, most any group (electron withdrawing or donating) such as $SCOCH_3$, $OCOCH_3$, C_6H_5CO, C_2H_5CO, CH_3CO, Br or CH_3 in the 2-position has little effect on the formation of the photoperoxide provided that the meso-positions contain an aromatic group such as phenyl. These compounds liberate about 90 per cent of the theoretical amount of oxygen, except in the case of CH_3 which yields only 60 per cent. The 2-methyl-3-acetyl-9,10-diphenylanthracene, however, forms a stable 9,10-peroxide which on thermal decomposition (160°) yields over 90 per cent of its oxygen[11]. In many cases, the original compound is regenerated.

The effect of groups in the 1-position of 9,10-diphenylanthracene on photoperoxidation is more pronounced. The 1-halogen derivatives yield a 9,10-photoperoxide in the normal manner and are dissociated at 175-200° to yield only about 70-77 per cent of the theoretical amount of oxygen. In the case of 1-dimethylamino-9,10-diphenylanthracene, however, only resins result on irradiation probably due to the sensitive nature of the amino group toward oxidation[12].

Of particular interest is the formation of transannular peroxides in more complex anthracene-type systems than outlined above. Meso-diphenyldianthryl and 4,9-diphenylthiophanthrene do not afford peroxides which could be isolated. In the former case, the uptake of oxygen is extremely slow showing no tendency for peroxide formation[3], and in the latter case only a resin results on attempted isolation of a peroxide[14].

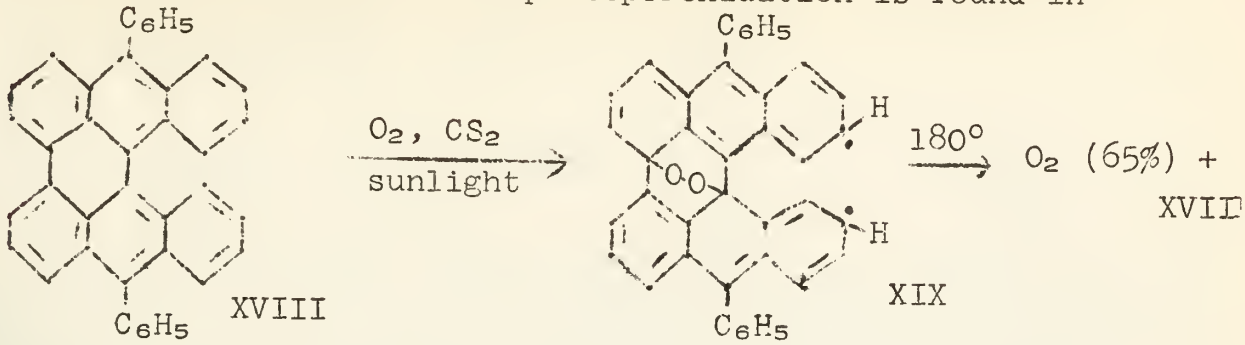
Hetero-cerodianthrone is photo-oxidized in three seconds in sunlight resulting in the formation of the transannular peroxide which decomposes at 150° to liberate 95 per cent of its oxygen[15]. If, however, the irradiation is prolonged and the solvent used is pyridine, a dihydroxide is isolated rather than a peroxide. The explanation given is that this particular photoperoxidation involves an equilibrium between a dihydroxide and the peroxide.



Phenylceroxene (XVI) is so sensitive to light that photoperoxidation must be carried out in very dilute solutions in semi-darkness, and the irradiation must be stopped before the reaction is complete (disappearance of color). The peroxide XVII dissociates at 140° (as compared with 180° for meso-diphenylanthracene) but liberates only 50% of the theoretical amount of oxygen and 20% CO_2[16].

Perhaps the only diphotoperoxide known in the anthracene series at present is that produced on irradiation of meso-tetraphenyl-1,1'-bianthryl. Each peroxide bridge occurs in the 9,10- and 9',10'-positions[17].

The combination of two structures, one which undergoes ready oxidation to give a diphotoperoxide and the other which is not sensitive at all to photoperoxidation is found in

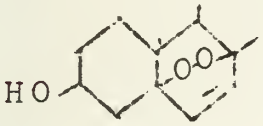


meso-diphenylhelianthrene (XVIII) which is the most photosensitive substance thus far studied. Reaction is complete in a fraction of a second yielding a yellow monoperoxide. This is the first instance in which a colored peroxide is formed. It contains only one mole of oxygen and appears to be a double free radical. The structure XIX seems most probable on the basis of models and color[18].

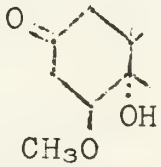
From theoretical studies[19] of bond lengths and free valences in the ground and excited states of anthracene and other polynuclear hydrocarbons, it is concluded that those positions that are already reactive in the ground state become even more reactive under the influence of light.

Photoperoxidation in the Alicyclic (Steroid) System.

One requirement for the formation of transannular peroxides in alicyclic compounds appears to be that the system contain a conjugated diene-type structure. The formation of transannular peroxides in the steroid series was first encountered in the studies on the relation of ergosterol to vitamin D. Windaus and Brunken[20] found that when ergosterol was dissolved in alcohol containing a small amount of eosin as a sensitizer (oxygen bubbled through) and the solution exposed to radiation from a 200-watt filament lamp, there is produced a crystalline ergosterol peroxide. The structure of the peroxide is still open to question, but Fieser's postulated structure (XX) appears to fit all the chemical facts[21].



XX

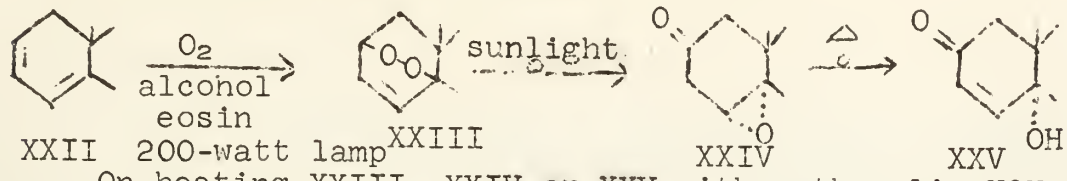


XXI

Since the structure of ergosterol peroxide is still a controversial issue, and the physical and chemical data are reviewed in Bergmann's and McLean's article[1], it will not be covered in this report.

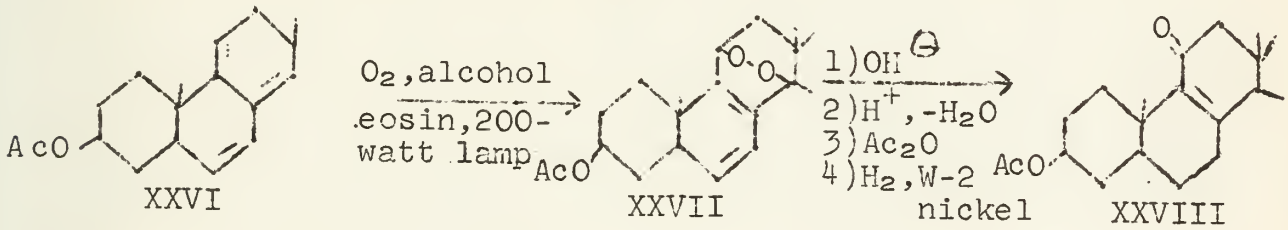
The photoperoxidation of 2,4-cholestadiene (XXII) has been studied[22] and the structure of the peroxide (XXIII) determined quite conclusively. The product obtained depends on the light source used for irradiation. Exposure of a solution (oxygen bubbled through) of 2,4-cholestadiene in alcohol containing a small amount of eosin to a 200-watt tungsten lamp results in the formation of a crystalline peroxide XXIII, m.p. 113-114°, $[\alpha]_D$ + 48.3°. Exposure under similar conditions, except using sunlight

in place of the tungsten lamp, results in the formation of a crystalline compound XXIV, m.p. 166-168°, $[\alpha]_D$ + 141°, which is not a peroxide. The peroxide obtained from tungsten lamp irradiation if exposed to sunlight produces the same non-peroxide substance XXIV. On further study[23] it was found that the reactions which take place are as follows:



On heating XXIII, XXIV or XXV with methanolic KOH, the same ketone XXI is obtained. This course of reaction is not unusual for peroxides of this type. According to the findings of Kornblum and De La Mare[24], dialkyl peroxides containing a hydrogen atom on the α-carbon attached to the peroxide linkage are cleaved by alkali to a ketone and a tertiary alcohol. The α,β-unsaturated ketone XXV can then undergo a Michael-type condensation with methanol to give XXI.

Photoperoxidation has recently afforded a new route to 11-oxygenated steroids. Leuback[25] has found that $\Delta^{6,8(14),9(11),22}$-ergostatetraen-3β-ol acetate (XXVI) undergoes photoperoxidation as shown



above. By alkaline cleavage of (XXVII) dehydration, reacetylation and selective reduction, the well-known cortisone intermediate (XXVIII) was obtained.

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5-AMINO-TETRAZOLE AND ITS ALKYL AND ARYL DERIVATIVES

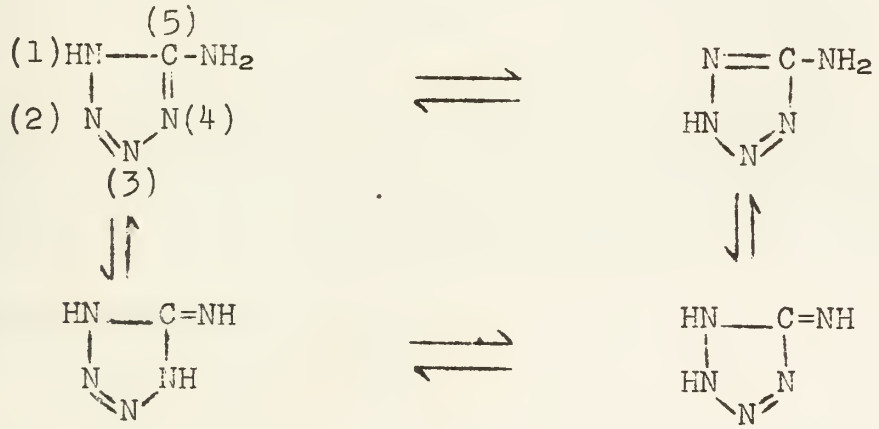
Reported by Harold H. Hughart October 30, 1953

5-Amino-Tetrazole

Since Thiele and Ingle[1] first reported the preparation of 5-amino-tetrazole, it has been the subject of many investigations, chiefly because of its potential value as an explosive and because of the interesting chemical and physiological properties of some of its derivatives.

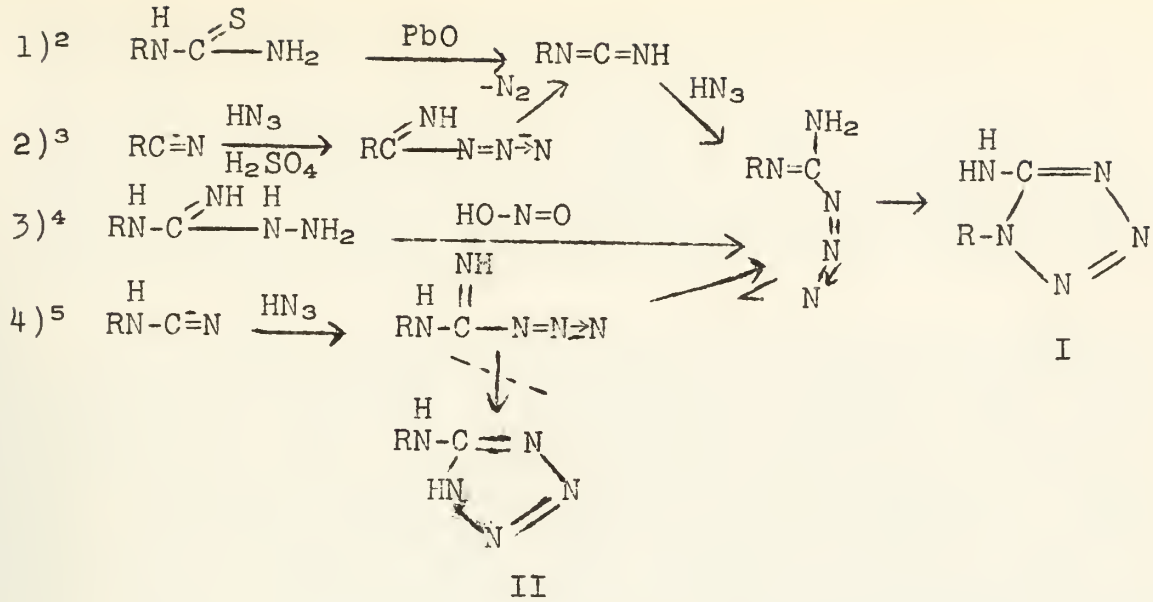
The tetrazole ring is remarkably stable and 5-aminotetrazole is neither readily reduced nor easily hydrolyzed in acid solution. Aqueous alkali and alkaline oxidizing agents, however, cleave the ring to produce NaN_3, N_2H_4, and smaller fragments. As is the case with all aminotetrazoles unsubstituted in the 1-position, 5-aminotetrazole is a moderately strong acid.

Its basic properties are scarcely apparent, and the usual amine reagents react only under forcing conditions, although a rather stable diazonium compound is formed. Thiele and Ingle have described a variety of products resulting from attempts to methylate, ethylate, and benzylate 5-aminotetrazole, the true structures of which require confirmation in most instances. This is not surprising, considering the tautomeric possibilities in this compound.



1-Substituted Derivatives

Many of Thiele's compounds have been synthesized in unequivocal manner by ring closure of suitably substituted acyclic intermediates. 1-Alkyl and 1-aryl derivatives have been prepared by the following reactions.

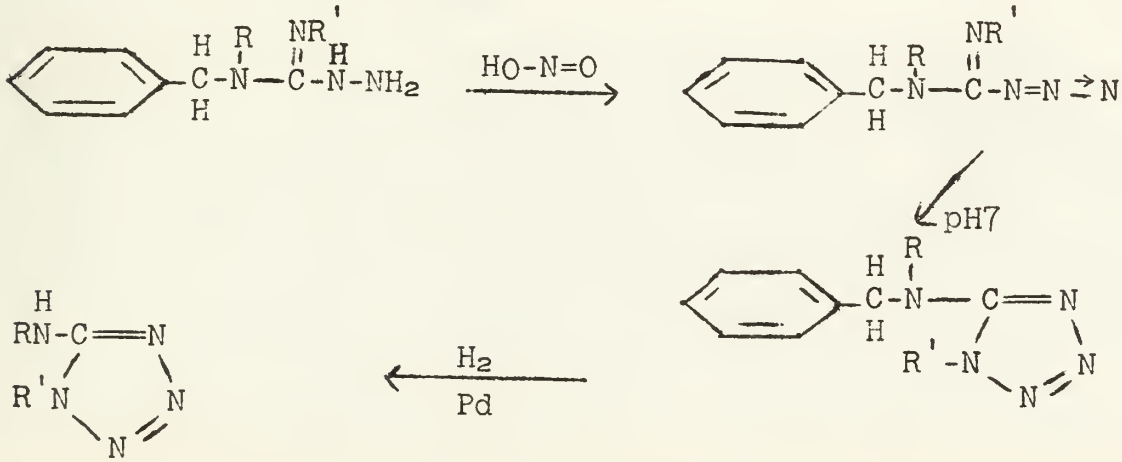


It is interesting that in all cases the postulated reaction mechanism proceeds through the guanyl azide. Only in the case of reaction (3) has this intermediate been isolated; here it can be obtained as a crystalline salt showing the expected azide properties. As shown in reaction (4), monosubstituted guanylazides exist in two tautomeric forms which by ring closure yield two different tetrazoles. Surprisingly, all these reactions yield the 1-alkyl- or 1-aryl-5-aminotetrazole (I) as the major product. The second isomer has seldom been isolated or detected, although when R is the nitro group, 5-nitro-aminotetrazole is the main product.[6]

In a recent series of experiments, Finnegan, Henry, and Lieber[4] have isolated two compounds from several guanyl azides prepared by methods (2) and (3). The minority isomers were precipitated from solution as their insoluble copper salts and their structure as 5-substituted aminotetrazoles was established by the following synthesis.

5-Substituted Derivatives

R=alkyl or aryl; R'=H



Compounds prepared in this way were identical with the corresponding compounds liberated from the copper salts by H_2S. When, in this reaction sequence, R' is alkyl or aryl, and R is an alkyl group, 1,5-disubstituted compounds are obtained which must have the formula III. Finnegan, Henry, and Lieber[4] have prepared a series of six of these compounds. They closely resemble the mono-substituted tetrazoles I in being solids of rather high melting point and neutral reaction in water solution.

Previously, many disubstituted tetrazoles were prepared by direct alkylations[1,6] (best by alkylation of the mono-substituted tetrazoles I) and assigned structure III. These compounds act like secondary amines, forming nitroso compounds which give a positive Liebermann's test, and reacting with alkylating agents to replace the last hydrogen. Their water solutions are basic, and they are liquids or low-melting, distillable solids. Their true structure, though unknown, is not that which has been assigned, since the properties of the six compounds prepared by cyclization differ markedly from the corresponding members of this series.

Rearrangements[4]

It has been observed that the 5-alkyl-aminotetrazoles are structurally unstable at elevated temperatures and rapidly and quantitatively isomerize to the corresponding 1-alkyl-5-aminotetrazoles when heated at 180-190°. Under these conditions, 1-phenyl-5-aminotetrazole isomerizes in the opposite direction to form 5-anilinotetrazole. Several disubstituted tetrazoles have also been isomerized. Thus, 1-methyl-5-anilinotetrazole is obtained from 1-phenyl-5-methylamino-tetrazole. It is unlikely that this isomerization involves group migrations. More likely it is due to a ring opening to the substituted guanylazide and a recyclization of the latter to the thermodynamically more stable tetrazole, or to an equilibrium in which the more stable tetrazole predominates. The idea of an equilibrium is supported by the observation that certain tetrazoles, e.g. 1-methyl-5-benzylamino-, can only be partially isomerized, and even in the cases where the reaction is rapid and quantitative, a trace of starting material is always present.

No explanation is offered why the 1-phenyl-5-amino-tetrazole is formed predominantly in the low temperature cyclization in aqueous solution, whereas the thermodynamically stable form appears to be 5-anilinotetrazole. However, the high temperature behavior of these compounds is consistent with the idea that the cyclization of the substituted guanylazides should take place predominantly on the expected nucleophilic centers. This also accounts for the isomerization of the 5-alkylamino compounds. Furthermore, so far as data have been accumulated, the tendency for 1-aryl-5-amino-tetrazoles to rearrange to the 5-aryl aminotetrazoles decreases with introduction of ortho or para alkyl or alkoxy groups into the benzene nucleus.

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The Mechanism of the Ketonic Pyrolysis of Calcium Carboxylates

Reported by Gordon R. Johnston November 6, 1953

The thermal decomposition of the salts of carboxylic acids to produce carbonyl compounds has been known for quite some time. In addition to pyrolyzing the salt, the free acid can react similarly by passing its vapor over the metal oxide at elevated temperatures. This synthesis once constituted the primary method for the manufacture of acetone from the gray acetate of lime from pyroligneous acid.

Due to early reports in the literature regarding the inability to ketonically decarboxylate certain acids which did not have alpha hydrogens (1, 2, 3), Neunhoeffer and Paschke (3) formulated a mechanism which required a hydrogen on the alpha carbon. They proposed that in the first step of the pyrolysis of calcium acetate a rearrangement occurs to give the beta keto acid or its salt:

$$(CH_3COO)_2Ca \rightarrow CH_3COCH_2COOCaOH.$$

This intermediate could then decompose to give acetone and calcium carbonate, or, in a side reaction, denydrate in its enolic form to a neutral enolcarboxylate:

$$CH_3C(OH){=}CHCOOCaOH \rightarrow CH_3C{=}CHCOOCaO + H_2O.$$

Without water or acid this latter salt could no longer decompose to give a ketone. These workers found that the yield of ketone is increased in the presence of steam or excess acid, and that anhydrous barium adipate gives less cyclopentanone and more cyclopentene than a less carefully dried sample. This would tend to support their mechanism. They also discovered that excess base, above the required catalytic amount, lowers the decomposition temperature but favors the formation of by-products. The reaction appears to be reversible. When acetone, water vapor, and carbon dioxide were heated at 350° for six days in an oxygen-free atmosphere, acetic acid was detected.

In 1950, Miller, Cook and Whitmore (4) reported on the decarboxylation of trimethylacetic and isobutyric acids. The former reaction is the first account of an acid containing no alpha hydrogens being successfully pyrolyzed to a ketone. Trimethylacetic acid was passed over aerogel thoria catalyst at 490°. t-Butyl isobutyl ketone (15%) and t-butyl methyl ketone (9%) were the major liquid products together with trimethylacetaldehyde (3%) and crotonaldehyde (3%) and unreacted trimethylacetic acid (21%). The chief products of the reaction were t-butyl isobutyl ketone and carbon dioxide, with all other gaseous and liquid products being decomposition products of this ketone. The following mechanism was offered for the formation of t-butyl isobutyl ketone (Fig. 1, R=CH_3):

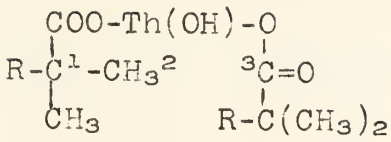
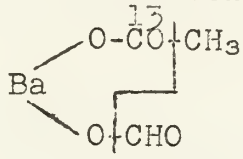


Fig. 1

the formation of di-t-butyl ketone is sterically hindered because of the fact that carbon-3 cannot approach carbon-1. Therefore, a reaction might occur between carbon-2 and carbon-3, probably by an aldol type of condensation through a seven membered ring intermediate. This intermediate may then decompose to the thorium salt of a gamma keto acid which may then be decarboxylated to the ketone. Under similar reaction conditions, isobutyric acid gave 50% diisopropyl ketone and 5% n-propyl isopropyl ketone. In this case, however, (Fig. 1, R=H) carbon-1 can react with carbon-3 by an aldol condensation to give diisopropyl ketone. The n-propyl isopropyl ketone is formed by the condensation between carbon-2 and carbon-3. In general, acids which have no alpha hydrogens may be ketonically decarboxylated with reaction occuring at the beta carbon yielding unsymmetrical ketones, while acids which have both alpha and beta hydrogens may react both at the alpha and beta carbons, with reaction at the alpha carbon being favored. Miller, Cook and Whitmore also concluded that the catalyst acted as an orientating agent for the two acid fragments.

Bell and Reed (5) have postulated a free-radical mechanism for this reaction. They investigated the pyrolysis of a mixture of barium acetate enriched with C^{13} in the carboxyl group and barium formate. It was found that the residual barium carbonate was enriched in C^{13}, while the acetaldehyde formed had a normal enrichment. The reaction scheme is represented as follows:



$\rightarrow \quad CH_3CHO + BaC^{13}O_3.$

They postulated the following mechanism: ba=1/2Ba

1. Chain initiation: $CH_3COOba \rightarrow CH_3\cdot + \cdot COOba.$
2. Aldehyde formation: $CH_3\cdot + HCOOba \rightarrow CH_3CHO + \cdot Oba.$
3. Acetone formation: $CH_3\cdot + CH_3COOba \rightarrow CH_3COCH_3 + \cdot Oba.$
4. Chain continuation: $CH_3COOba + \cdot Oba \rightarrow CH_3\cdot + ba_2CO_3\cdot$
5. Chain termination: $2CH_3\cdot \rightarrow C_2H_6$, etc.
   $2\cdot Oba \rightarrow (Oba)_2\cdot$
   $\cdot COOba + \cdot Oba \rightarrow ba_2CO_3\cdot$

Recently, Lee and Spinks (6) have undertaken research on this reaction. They carried out pyrolyses using mixtures of calcium acetate, enriched with C^{14} in the carboxyl group, and an equimolar quantity of unlabelled calcium benzoate,

p-toluate, phenylacetate, or n-valerate, as well as carboxyl-enriched calcium benzoate and an equimolar quantity of ordinary calcium formate, acetate, or propionate. The mixed carbonyl compounds obtained were converted into their semicarbazones and their radioactivity measured. The results shown in Table I indicate the ease of loss of carboxyl to be acetate > phenylacetate > n-valerate > formate > benzoate.

Table I

Reactants		% of original activity in unsymmetrical ketone	
		Run I	Run II
Acetate-C^{14}	+ benzoate	1.4	1.5
"	+ p-toluate	1.3	1.6
"	+ phenylacetate	33.3	33.4
"	+ n-valerate	19.1	18.7
Benzoate-C^{14}	+ formate	90.7	92.6
"	+ acetate	101.4	101.4
"	+ propionate	100.9	101.6

Lee and Spinks discounted the mechanisms of Neunhoeffer and Paschke (3) and of Miller, Cook and Whitmore because of the facts that a condensation reaction cannot explain the formation of diaryl ketones from aromatic acids and that aldol condensations usually don't take place between salts of carboxylic acids. They also disfavored the free-radical mechanism because of the fact that acetate and formate both lose their carboxyl groups easier than benzoate. In the former case, the benzyl radical should be more stable than the methyl radical, and in the latter the energy of the carbon-hydrogen bond is greater than the carbon-carbon bond. The authors first formulated a mechanism involving an acyl carbonium ion:

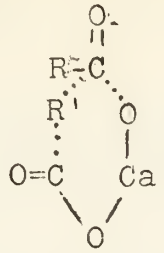
$$\mathrm{RCOOM} \rightarrow (\mathrm{R{-}C{=}O})^{+} + \mathrm{MO}^{-};$$
$$(\mathrm{R{-}C{=}O})^{+} + \mathrm{R'COOM} \xrightarrow{\text{slow}} \mathrm{RCOR'} + \mathrm{M}^{+} + \mathrm{CO_2}.$$

The second step is a rate-controlling S_E2 type of decarboxylation. In summarizing some of their supporting arguments, acetate should lose its carboxyl group easier than benzoate because of the favorable backside attack of $C_6H_5\text{-}C\overset{+}{=}O$ on acetate, as opposed to the frontal attack of $CH_3\text{-}C\overset{+}{=}O$ on benzoate. Similarly, steric factors might favor attacks by $C_6H_5CH_2\text{-}C\overset{+}{=}O$ and $CH_3(CH_2)_3\text{-}C\overset{+}{=}O$ on acetate rather than the opposite processes. In addition, the attack of the phenylacyl carbonium ion on formate is probably of sufficient importance to overcome the high energy necessary to rupture the carbon-hydrogen bond.

Because of the objection that the formation of an onium ion is usually slow compared to its reactivity, a concerted intermolecular mechanism was also postulated:

$$\mathrm{MO{-}\overset{\overset{R'}{|}}{\underset{\underset{O}{\|}}{C}}} + \mathrm{RCOOM} \rightarrow \mathrm{MO\cdots\overset{\overset{R'}{|}}{\underset{\underset{O}{\|}}{C}}\cdots R\cdots COOM} \rightarrow \mathrm{RCOR'} + \mathrm{M_2CO_3}.$$

A concerted intramolecular mechanism through a cyclic intermediate (Fig. 2) was hypothesized for the reaction of mixtures of aliphatic and aromatic salts of bivalent metals:



,

Fig 2

in which R is aryl and R' alkyl. This latter intramolecular process appears to be the most probable mechanism for the reaction according to Lee and Spinks.

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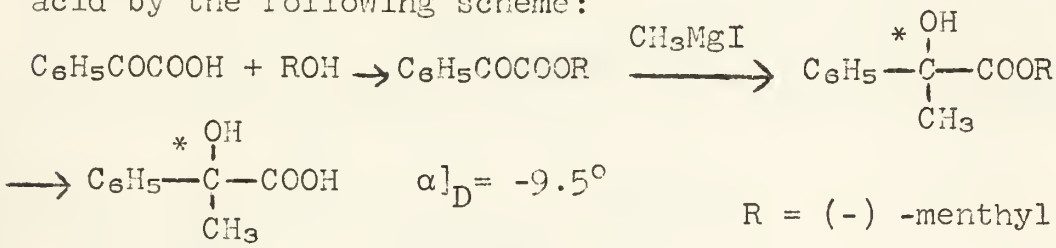
ASYMMETRIC INDUCTION WITH GRIGNARD REAGENTS IN OPTICALLY ACTIVE SOLVENTS

Reported by Roger H. Kottke November 6, 1953

The use of a Grignard reagent in a partial asymmetric induction was first reported nearly fifty years ago when McKenzie[1] prepared optically active methylphenylglycolic acid by the following scheme:



Turner[2] has recently made use of this type of procedure to prepare optically active gamma and delta keto-acids. Prelog[3] also used the same method in his proof of the absolute configurations of some naturally occurring optically active alcohols.

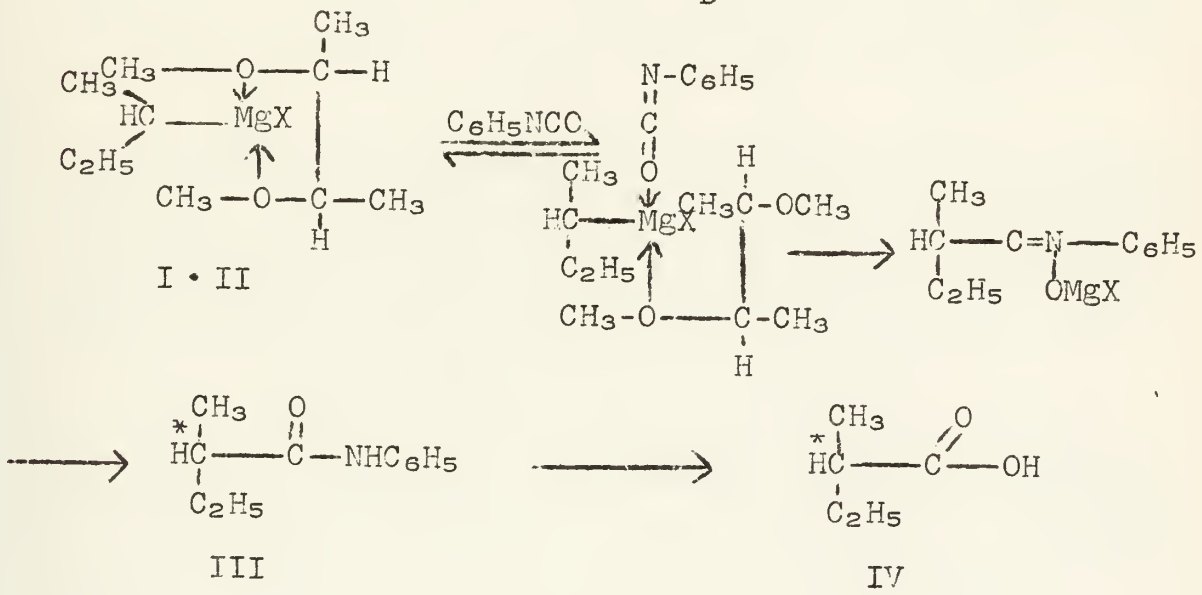
Partial asymmetric reductions have been accomplished with Grignard reagents. Vavon[4] using the Grignard reagent from pinene hydrochloride was able to reduce ketones to optically active secondary carbinols in yields as high as 69%. Moscher[5] reduced hindered alkyl ketones such as methyl t-butyl ketone with the Grignard reagent of an optically active alkyl halide as a method of substantiating the 6-membered ring transition state concept of Whitmore and George[6].

There have been various attempts to effect asymmetric induction by carrying out reactions in optically active solvents. As an example Walden[7] hydrolyzed inactive chlorosuccinic acid in (+) -amyl alcohol; as might be expected, no rotation of the hydroxy acid was observed. Betti and Lucchi[8] claimed the isolation of an optically active alcohol by the action of methylmagnesium bromide on benzaldehyde using (+) -bornyldimethylamine as a solvent. However, Tarbell and Paulson[9] in attempting to repeat this work were unable to prepare active methylphenylcarbinol and demonstrated that a decomposition product of the solvent was active; rotation was observed whether or not benzaldehyde was added to the reaction mixture. They further reported that similar reactions carried out in partially resolved sec-butyl ether gave only optically inactive carbinols.

It is known that the addition of dioxane to a Grignard reagent will precipitate RMgX, but the use of other diethers as solvents for Grignard reactions has not been thoroughly investigated[10]. Recently Wright[10] has shown two such diethers to be satisfactory for Grignard reactions, 1,2-dimethoxyethane and 2,3-dimethoxybutane. The yields of Grignard reagents in dimethoxyethane were found to be comparable to these in diethyl ether. It is superior in at least one instance; a Grignard reagent can be prepared from 6-chloro-2,2,6-trimethylcyclohexanone in dimethoxyethane but not in diethyl ether[11]. Only slightly specialized conditions

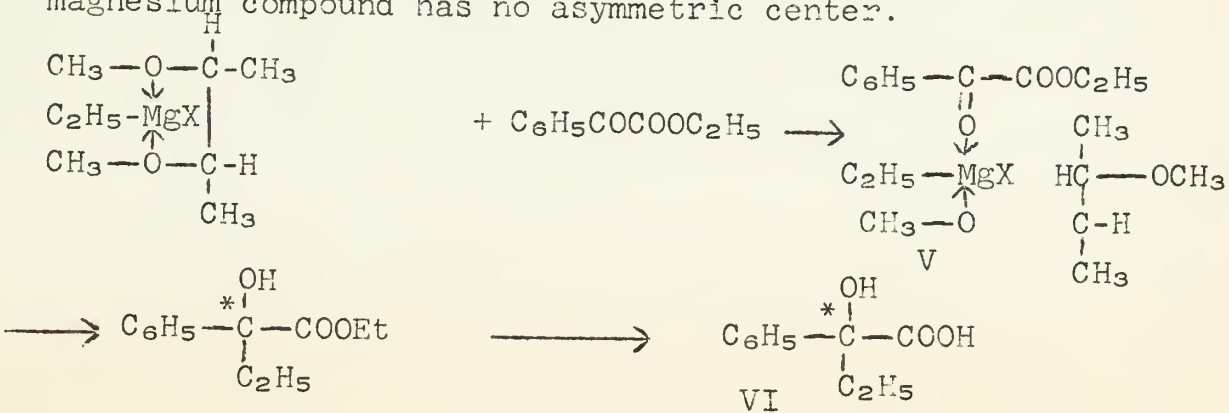
are required for reagent formation in these diethers. A high speed stirrer with a sharpened stainless steel blade keeps the magnesium reasonably clean and maintains a fast reaction rate. Benzene or toluene is often used with dimethoxybutane to prevent the precipitation of magnesium halide that occurs when the diether is used alone.

Wright has demonstrated that slight optical activity can be introduced into addition products of asymmetric Grignard reagents with carbonyl compounds, due to the coordination complex that (+) -2,3-dimethoxybutane (I) forms with the reagent. Phenyl isocyanate was added to a 2-chlorobutane Grignard reagent (II) in pure I and an 80% yield of 2-methylbutanoylanilide (III), $\alpha]_D$ + 0.34° was obtained.



Hydrolysis of III gave 2-methylbutanoic acid (IV), $\alpha]_D$+0.29°, corresponding to an asymmetric induction of about 2%. By carbonation of the reagent-ether complex I·II, an 85% yield of IV, $\alpha]_D$-0.21° was produced. Treatment of I·II with benzoyldurene and mercuric chloride gave slightly active products, but in total yields of only 10 and 20%, respectively. Addition of formaldehyde to I·II produced inactive 2-methylbutanol in 18% yield.

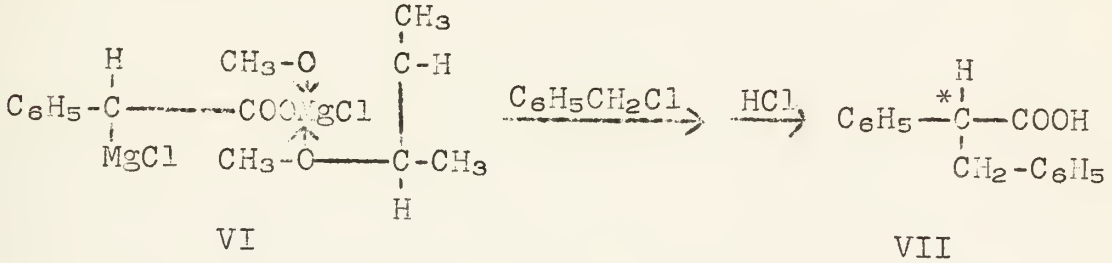
In another type of experiment, similar to that of McKenzie described above, ethyl benzoylformate was treated with ethylmagnesium bromide in (+) -dimethoxybutane, and the resulting phenethylglycolic acid (VI) had a specific rotation, $\alpha]_D$+1.18°, corresponding to about 5% asymmetric induction. The intermediate V is postulated since the organomagnesium compound has no asymmetric center.



The generally accepted theory that the configuration of an optically active Grignard reagent where the asymmetric center is linked directly to magnesium is not retained,[12,13,14] was again demonstrated by observing that the products formed by the addition of 0.5 and 1.0 molar equivalents of phenyl isocyanate to the Grignard-ether complex I·II had the same optical rotation. If configuration had been retained, the addition of a full molar amount of phenyl isocyanate would have given an optically inactive product.

Coupling reactions have been considered as involving free radicals[15,16]. Several coupling reactions were carried out and no optical activity was observed in any of the products. If free radicals are involved, the active solvent would not be expected to participate in the reaction, and no optical rotation would be observed. Thus, these results are not contradictory to the free radical concept.

However, in the coupling reaction between the Grignard reagent from phenylacetic acid and benzyl chloride, carried out in (+) -dimethoxybutane, optically active 2,3-diphenylpropanoic acid (VII), $\alpha]_D$ +1.52° was isolated. This result is plausible if dimethoxybutane is assumed to coordinate with the salt linkage in the intermediate VI, the reaction thus resembling those carried out by McKenzie[1,17].



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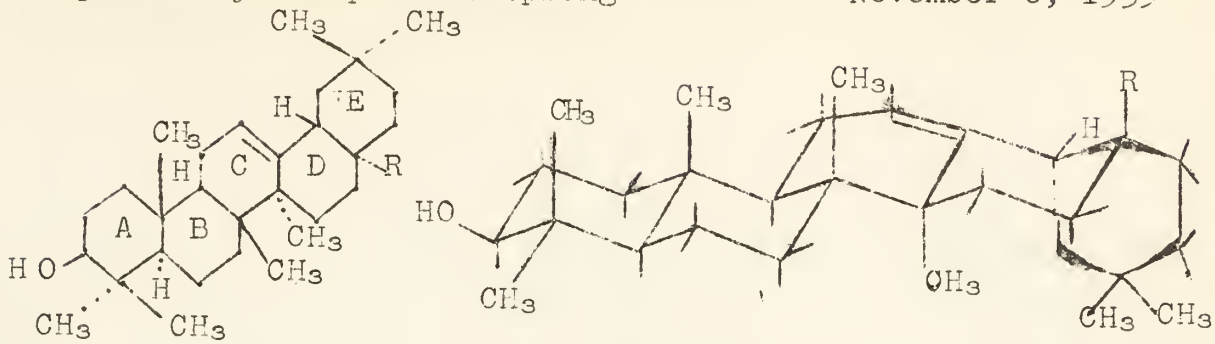
THE STEREOCHEMISTRY OF β-AMYRIN

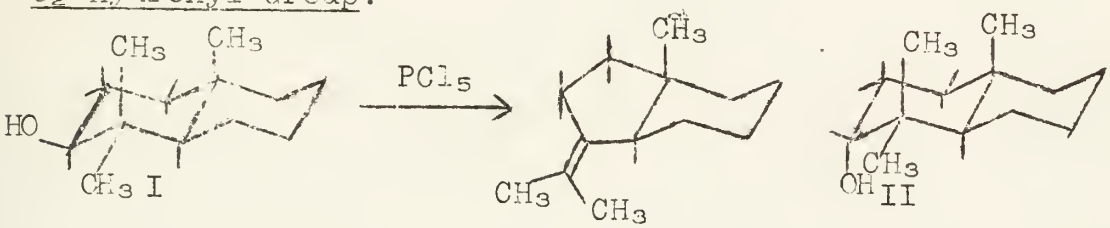
Reported by Joseph J. Ursprung November 6, 1953



β-amyrin (R=CH_3)
Oleanolic acid (R=COOH)

In recent years the stereochemistry of a large number of triterpenes belonging to the β-amyrin group has been elucidated. It is the object of this seminar to present the arguments supporting the stereochemical formulation depicted above. Most of the work has been done with oleanolic acid and β-amyrin but the arguments apply to all members of the β-amyrin group.

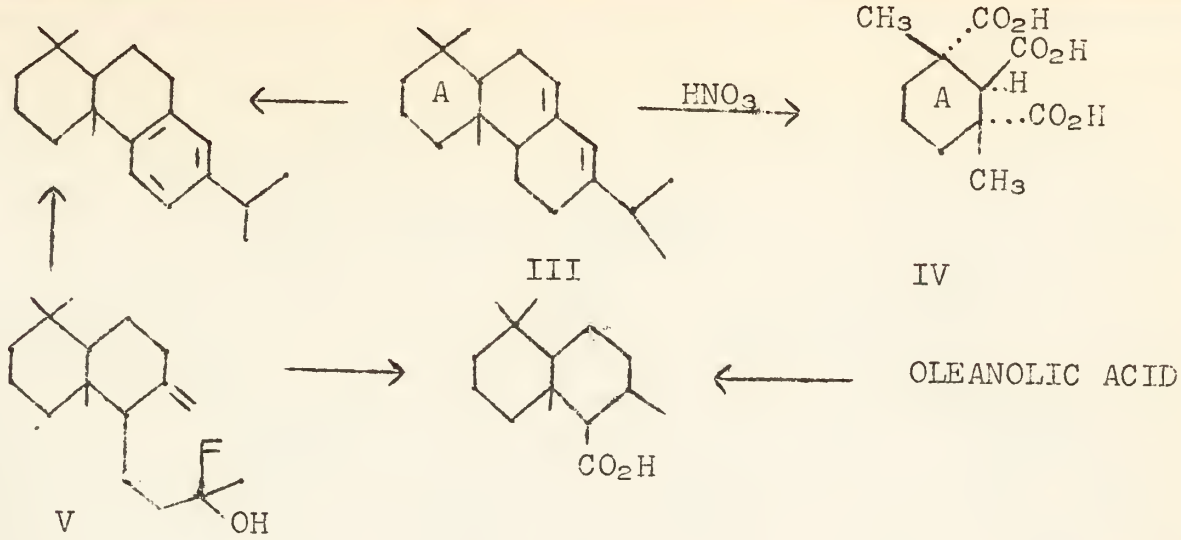
C_2-Hydroxyl Group.



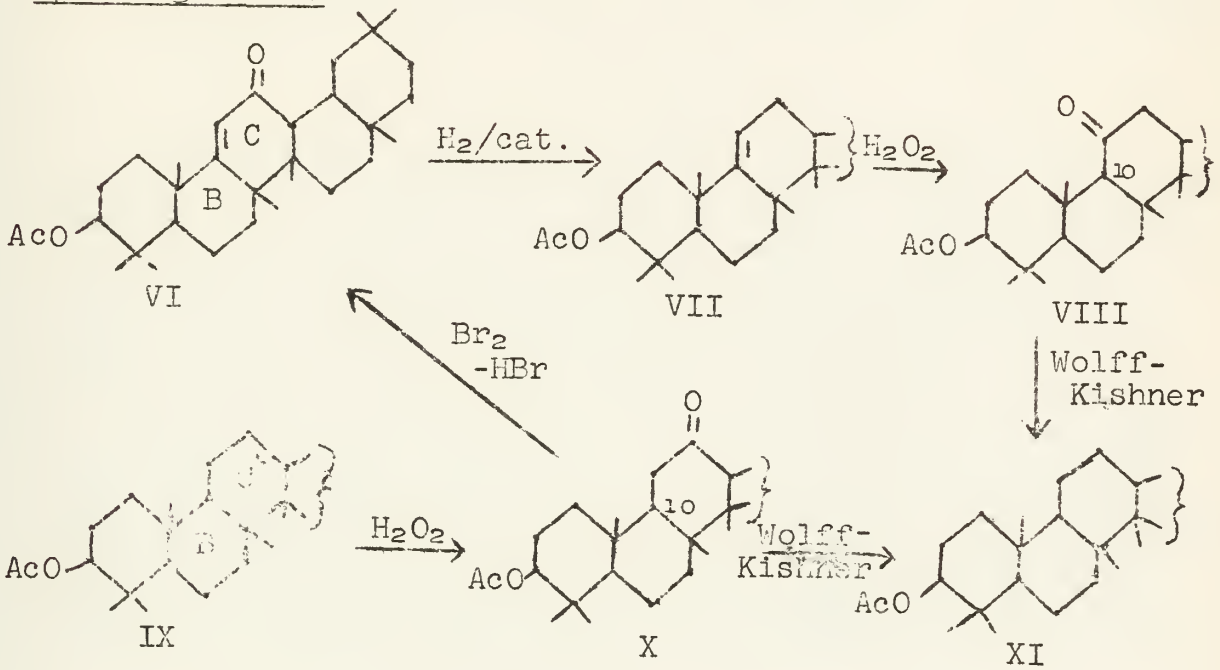
Molecular rearrangement accompanies dehydration of β-amyrin (I) while epi-β-amyrin (II) is dehydrated with ease to give the normal product. β-Amyrin acetate is also more readily hydrolyzed than epi-β-amyrin acetate. These observations, when subjected to conformational analysis[2], enabled Barton[1] to conclude that the hydroxyl was equatorial in β-amyrin and polar in epi-β-amyrin.

A/B Ring Fusion.

A study of the dissociation constants of the tricarboxylic acid IV, obtained by vigorous oxidation of abietic acid (III), enabled Barton and Schmeidler[3] to assign the configuration shown for the C_{11} acid. In view of the relationships which have been established between abietic acid and manool (V) on the one hand and oleanolic acid and manool on the other, as shown below, it can be concluded that, provided there is no inversion during the genesis of IV, rings A and B in oleanolic acid are trans fused. Barton[16] has also recently demonstrated that ring A must have the chair conformation rather than the alternate boat form.



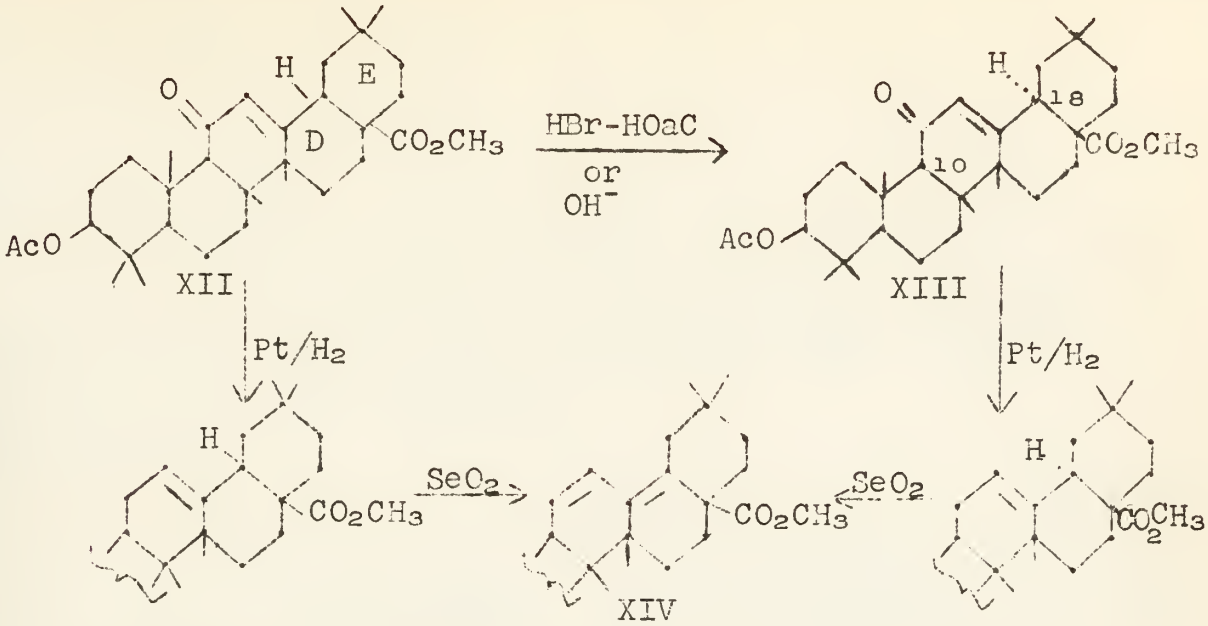
B/C Ring Fusion.



Formation of a new asymmetric centre in the conversion of iso-β-amyrenonyl acetate (VI) to iso-β-amyranonyl acetate (VIII)[4] indicates that the more stable union of rings B and C exists in VIII. Since the ketone VIII is not subject to epimerization at C_{10} and since the configuration at C_{10} is the same in β-amyrin acetate (IX), then the junction in β-amyrin must be the more stable one. It can be deduced that the more stable fusion is trans on the basis of Johnson's work[17] on the relative stability of fused ring systems and on the basis of the easy double bond formation at C_{10} on bromination.

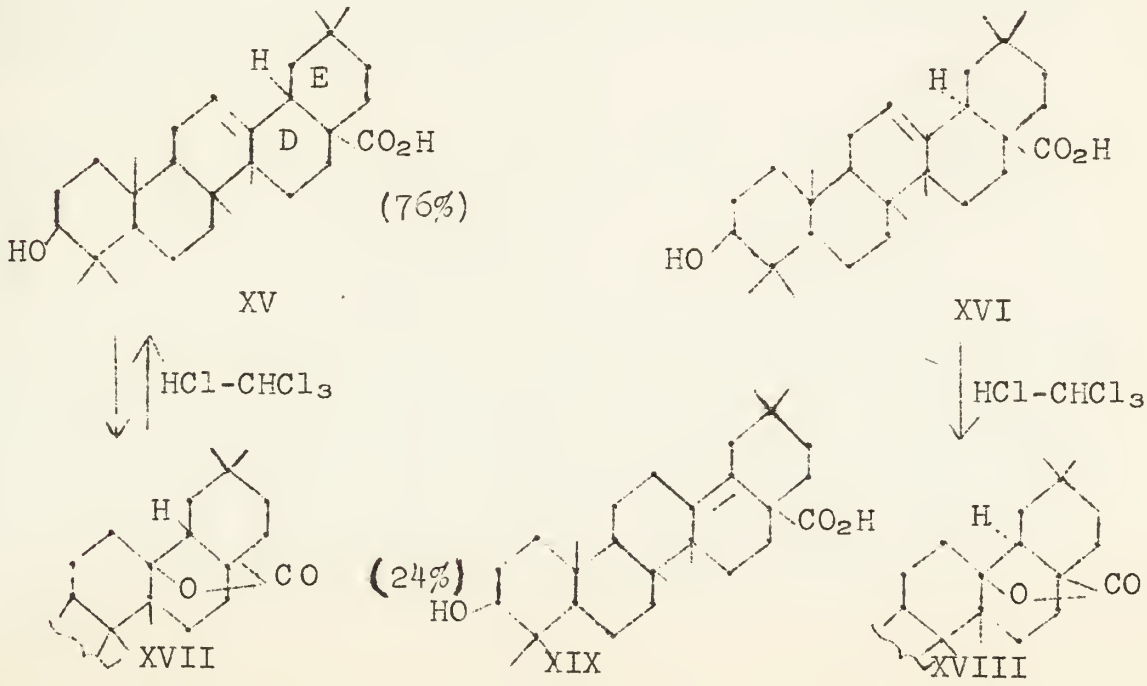
D/E Ring Fusion.

The ease of lactonization of oleanolic acid (XV) and its epimer (XVI) shows the carboxyl must be polar in the stereochemical sense[6]. This, however, still permits cis or trans fusion of rings D/E.



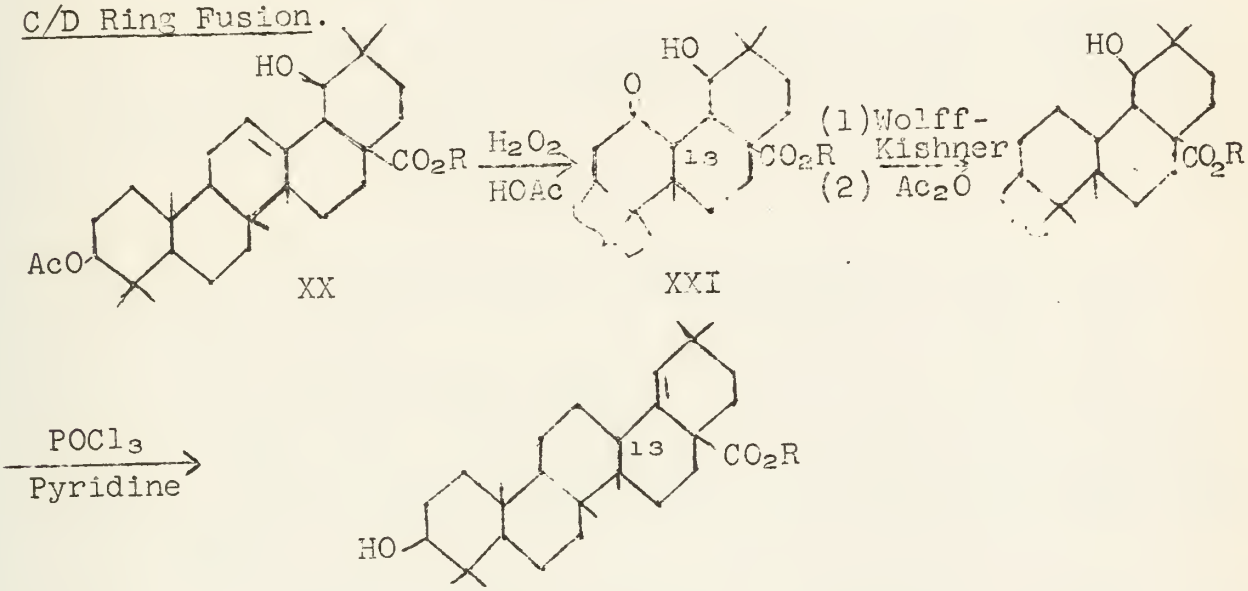
Strong acids[7] and strong bases[8,9,10] are known to isomerize methyl II-keto-oleanate acetate (XII). Asymmetric centres at C_{10} and/or C_{18} may be involved. Reduction of the two isomers followed by selenium dioxide oxidation gave the same produce (XIV) which could no longer by epimerized. Since C_{18} is the only asymmetric centre destroyed in this transformation, isomerization must have occurred at C_{18} to give the more stable trans decalin-type fusion[17].

More subtle evidence for a cis fusion of D/E was given by Barton[12]. When oleanolic acid (XV) or 18-iso-oleanolic acid (XVI) in chloroform solution is treated with hydrogen chloride the respective lactones are formed. With oleanolic acid the equilibrium mixture contains 76% free acid. The reaction velocity must be very large since equilibrium is established almost instantaneously whether the acid or its lactone is used as the starting compound[12].

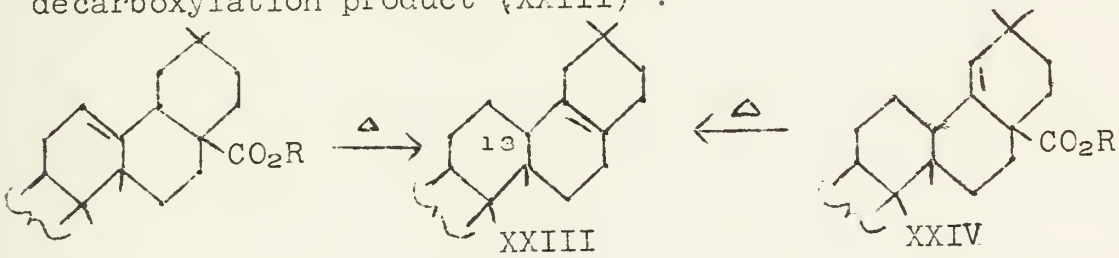


It had been shown earlier by Davy, Halsall and Jones[13] that the double bond position in δ-oleanolic acid (XIX) is much more stable thermodynamically than in oleanolic acid or in 18-iso-oleanolic acid. Complete equilibration of the lactone with the unsaturated acid might then be expected to give the thermodynamically stable δ-oleanolic acid (XIX). Despite this fact no δ-oleanolic acid was obtained even after long treatment with dry hydrogen chloride. This can only be explained on steric grounds. The formation of δ-oleanolic acid would not be favoured kinetically if it involves a cis elimination in an ionic reaction. Thus the hydrogen at C_{18} must be cis to the lactone oxygen and consequently cis to the carboxyl in oleanolic acid. A cis D/E ring fusion must then exist.

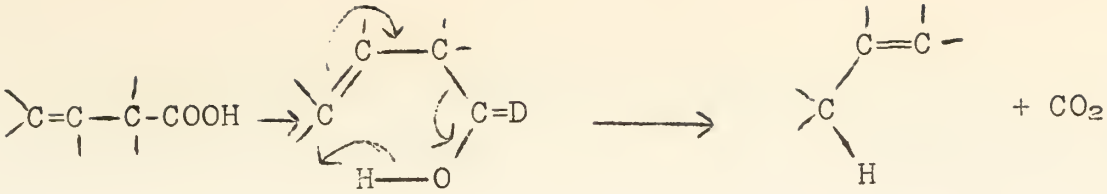
C/D Ring Fusion.



In the partial synthesis of morolic acid (XXII, R=H) from siaresinolic acid (XX, R=H)[15], the C/D junction is synthesized in such a way as to give the more stable trans fusion. The control of stereochemistry at C_{13} is possible by equilibration of the ketone XXI. Morolic acid has been experimentally linked with oleanolic acid through a common decarboxylation product (XXIII)[6].



Pyrolytic decarboxylation of β-γ-unsaturated acids is known to be accompanied by a shift of the double bond to the α-β-position[14]. Decarboxylation of oleanolic acid may be pictured as forming a lactone which opens on pyrolysis to give the β-γ-unsaturated acid and then decarboxylation may take place in the normal fashion. Barton[6] has shown the most probable mechanism for this reaction which involves a shift of the double bond to be one which has an intramolecular transition state with no formal separation of charge.



It follows, in accordance with this mechanism, that the hydrogen at C_{13} in compound XXIII and therefore in morolic acid (XXII) must be cis to the carboxyl position since the hydrogen at C_{13} in morolic acid is not affected by the decarboxylation. Relating morolic acid back to oleanolic acid it also follows that a trans-syn-cis relationship exists in rings C, D and E of dihydrooleanolic acid.

Correlation of the stereochemical evidence summarized in this seminar indicates that the most probable structure for oleanolic acid and therefore of all members of the β-amyrin group is the trans-anti-trans-anti-trans-syn-cis relationship as shown.

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STEREOISOMERISM OF YOHIMBINE AND PSEUDO-YOHIMBINE

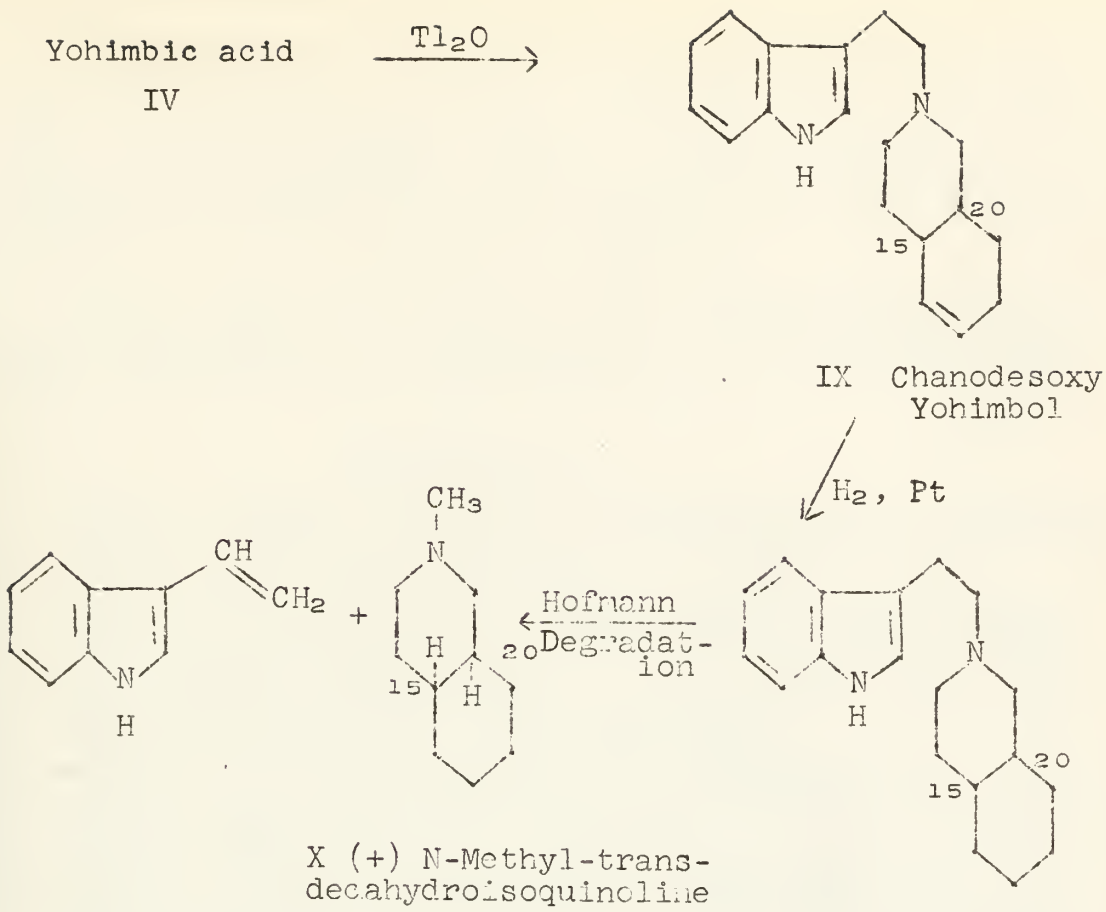
Reported by L. A. Miller November 13, 1953

The yohimbine alkaloids, obtained from the bark of the West African tree, "Corynantha Yohimbe," have long been emloyed by the natives as aphrodisiacs. The alkaloids, however have not had any widespread practical applications, although some use has been made of yohimbine itself as a sexual stimulant in veterinary medicine.[1]

Witkop, in 1943, described the correct basic structure of yohimbine (I), but he did not determine the configuration of the five asymmetric carbon atoms.[2] Pseudo-yohimbine (II), an isomer of yohimbine isolated by Karrer and Solomon from the mother liquors obtained in the preparation of yohimbine, has been shown to be a monobasic, indolic alkaloid, possessing, like yohimbine, an easily saponified methyl ester group and an alcoholic hydroxyl group.[3] Pseudo-yohimbine yields, on saponification with dilute alkali, pseudo-yohimbic acid (III), an isomer of yohimbic acid (IV) obtained from yohimbine in like manner. Oxidation of pseudo-yohimbic and yohimbic acids via the Oppenauer process results in the formation of two isomers, pseudo-yohimbone (V) and yohimbone (VI). Yohimbone is also obtained when pseudo-yohimbic acid is distilled from soda lime. Pseudo-yonimbone and yohimbone both give the same product, yohimbane (VII), when subjected to the Wolff-Kishner reduction.[4] The transformation of pseudo-yohimbic acid to yohimbone and the formation of yohimbane from either yohimbone or pseudo-yohimbone strongly indicates a difference in configuration at carbon 3 only, since this is the only center that could reasonably undergo change in alkaline media.

Pseudo-yohimbine and yohimbine, when subjected to dehydrogenation with lead tetraacetate, yield the same compound, tetradehydroyohimbine (VIII).[5,6] This clearly demonstrates that the sole difference between the two alkaloids lies in the configuration around carbon 3. However, in order to write the correct structure for pseudo-yohimbine and yohimbine, the configuration of the remaining asymmetric carbons must also be established.

Yohimbane contains asymmetric carbons at the 3, 15, and 20 positions. Witkop has shown, by degradation of chanodesoxy yohimbol (IX), obtained by distillation of a mixture of yohimbic acid (IV) and thallous oxide under reduced pressure,[2] that the D and E rings of yohimbine are joined in the trans position. Compound X has been shown to be identical with (+) N-methyl-trans-decahydroisoquinoline, thus establishing the relative configuration of carbons 15 and 20.[7,8]



The configuration of yohimbine and pseudo-yohimbine with regard to carbons 16 and 17 may be shown by a comparison of yohimbine with corynanthine (XI), the epimer of yohimbine at carbon 16. The difference in rate observed during saponification of yohimbine and corynanthine is quite striking, yohimbine being much more easily saponified than its epimer. This suggests that the carbmethoxy group of corynanthine must be less active than the corresponding group of yohimbine, an effect that can be directly attributed to the steric configurations of the respective molecules. It has also been found that the pKa's of corynanthine (6.05 and 8.44) are significantly higher than those of yohimbine (5.45 and 7.76) indicating that the carbmethoxy group of yohimbine must be in the least hindered or equatorial position while corynanthine must have a polar carbmethoxy group on carbon 16.[9,10]

Yohimbic acid, upon treatment with dilute alkali, loses water with the resultant formation of apo-yohimbol (XIII), while corynanthic acid (XII), when subjected to the same treatment, is both dehydrated and decarboxylated to yield apo-corynanthol (XIV), catalytic hydrogenation of which leads to yohimbane (VII).[4]

Since basic elimination reactions usually involve trans elements[9,10,11] the hydroxyl group in corynanthic acid must be trans to the carboxyl group, while the hydroxyl group of yohimbine must be trans with respect to the hydrogen on C_{16}. Thus, the relative configurations around carbons 16 and

17 can be written as indicated.

According to the theoretical considerations and experimental data acquired with analogous isocyclic systems[12], it is apparent that yohimbine, the most stable alkaloid, will contain the largest number of polar hydrogens.[11] Therefore, it may be assumed that the hydrogen on carbon 3 in yohimbine is polar, while the hydrogen on carbon 3 in pseudo-yohimbine is in the equatorial position.

On the basis of reactions and conformational analysis, the configuration of pseudo-yohimbine and yohimbine have been established on a firm basis.

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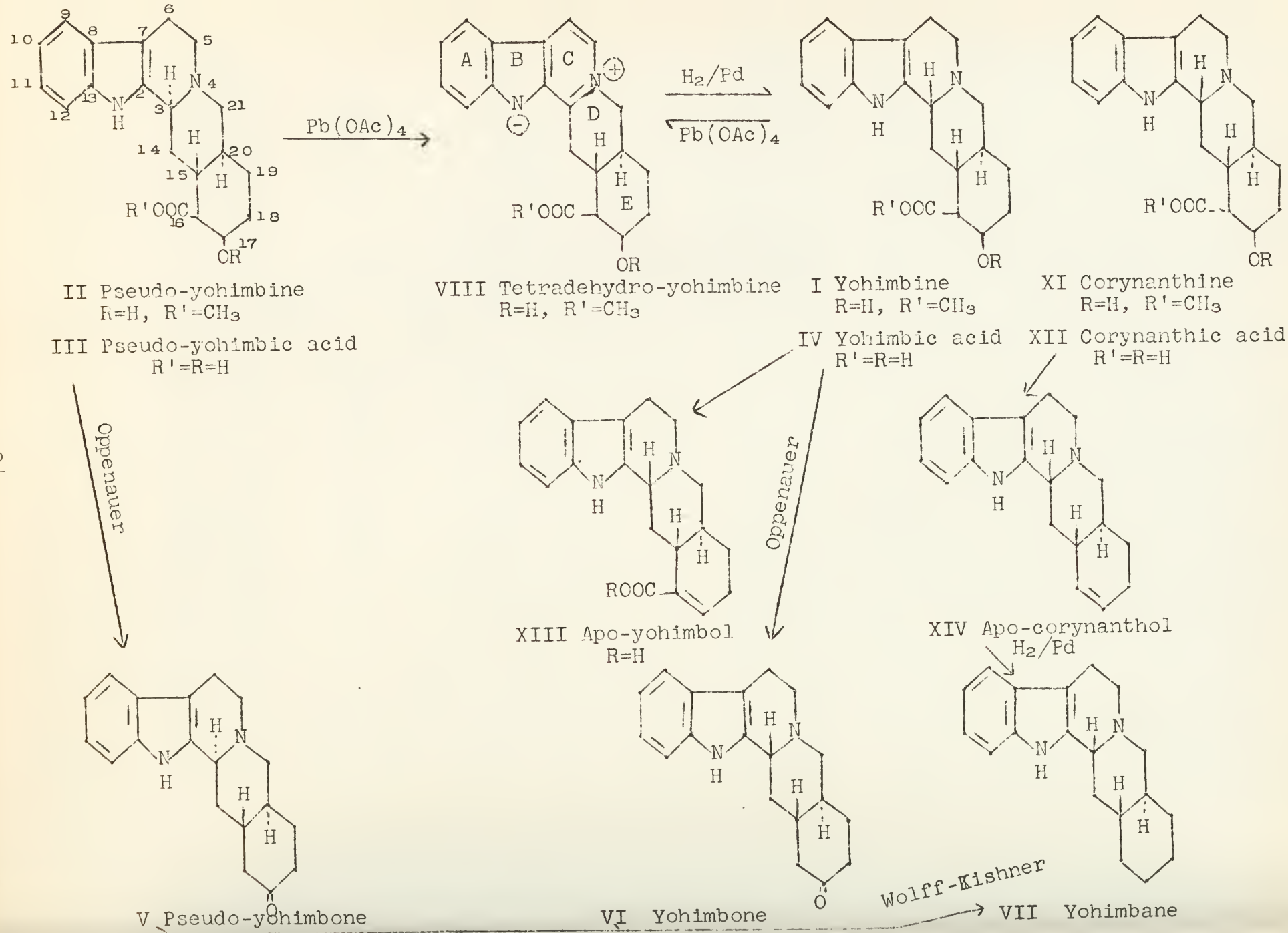
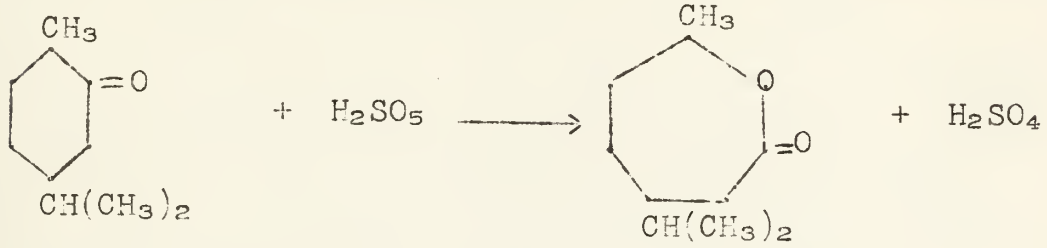

Pb(OAc)4
H2/Pd
Pb(OAc)4
II Pseudo-yohimbine
R=H, R'=CH3
III Pseudo-yohimbic acid
R'=R=H
VIII Tetradehydro-yohimbine
R=H, R'=CH3
I Yohimbine
R=H, R'=CH3
XI Corynanthine
R=H, R'=CH3
IV Yohimbic acid
R'=R=H
XII Corynanthic acid
R'=R=H
Oppenauer
Oppenauer
XIII Apo-yohimbol
R=H
XIV Apo-corynanthol
H2/Pd
V Pseudo-yohimbone
VI Yohimbone
Wolff-Kishner
VII Yohimbane

RECENT STUDIES ON THE BAEYER-VILLIGER REARRANGEMENT

Reported by Edwin J. Strojny November 13, 1953

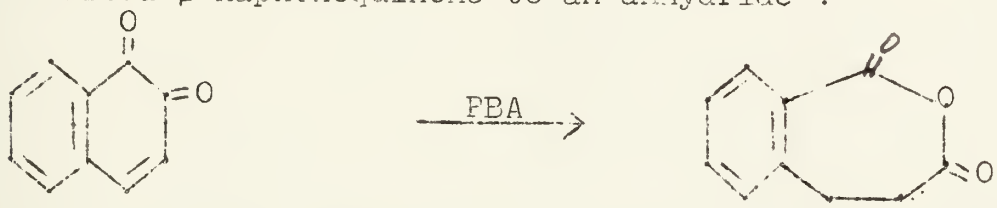
Peracids attack carbonyl groups to form transitional complexes which rearrange to form esters, lactones and (with α-diketones) anhydrides. Thus, Baeyer and Villiger[1], who were the first to employ the reaction, treated 2-isopropyl-5-methylcyclohexanone with Caro's acid and obtained the lactone indicated in the following equation:



Methylstyryl ketone, when treated with peracetic acid, rearranged to give an enol acetate[2]. Perbenzoic acid (PBA)

$$C_6H_5CH{=}CHCOCH_3 + CH_3CO_3H \longrightarrow C_6H_5CH{=}CHOCOCH_3$$

oxidized β-naphthoquinone to an anhydride[3]:



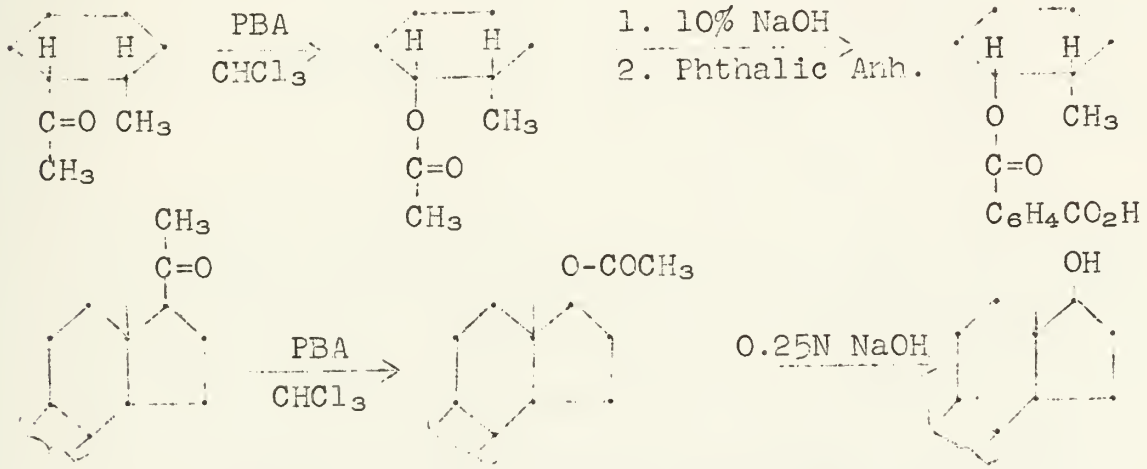
Numerous other examples may be found in a review by Leffler[4] and in a seminar by Figueras[5]. Recent studies have yielded additional information on reaction conditions, on migratory aptitudes of groups, on the stereospecificity of the rearrangement and on possible mechanisms.

As the most common procedure, the ketone is treated with a slight excess of perbenzoic acid at room temperature for about 7 days. The most common solvent is chloroform. E. Doering and Speers[6] used 40% peracetic acid in acetic acid in their studies on migratory aptitudes of aromatic groups. Balio and Almirante[7] prepared a number of substituted phenol acetates from substituted acetophenones by the use of a 20% excess of 22-28% peracetic acid containing 0.5% p-toluenesulfonic acid. Friess and coworkers[8,9], in studies on the effect of solvent on the rate of the reaction, used mixtures of chloroform and tetrachloroethane and chloroform and methanol. They noted that, as the polarity of the solvent increased, the rate of disappearance of perbenzoic acid increased. Friess[10] also found that this rate decreased slightly when moist chloroform was used. E. Doering and Speers[6] and Friess and coworkers[8,9,10] noted a general acid catalysis in the rearrangement. The action of peracetic acid on p-nitrobenzophenone to give phenyl p-nitrobenzoate in the presence of sulfuric acid illustrated a marked catalytic effect. In the absence of sulfuric acid, a 29% yield of the product was obtained after 336 hours. On addition of H_2SO_4,

a yield of 95% was obtained after half an hour. This was an exceptional case.

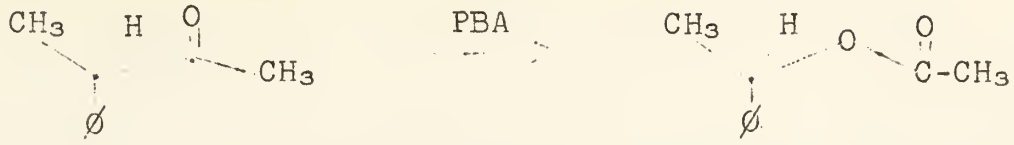
E. Doering and Speers[6] generalized, on studying the behavior of unsymmetrical ketones reported in the literature, that secondary and tertiary alkyl groups migrate to the oxygen more readily than primary groups. In studies on substituted benzophenones, they found the following migratory aptitudes: p-anisyl and p-tolyl > phenyl > p-chlorophenyl, p-bromophenyl, p-nitrophenyl and p-anilinium ion. In kinetic studies on the rate of disappearance of perbenzoic acid with a number of aromatic methyl ketones, Friess and coworkers[8,9,10,11] found that the reaction proceeded at a slower rate than when positive groups were present. In all of these reactions the aromatic nucleus only migrated. Friess and Farnham[12] noted, when studying the migratory aptitudes in acetophenone, acetylcyclohexane and phenylcyclohexyl ketone, that the phenyl group markedly decreased the rate of reaction with the peracid. With phenylcyclohexyl ketone, the migration ratio of cyclohexyl to phenyl was 5:1.

The migration was found to be stereospecific. cis-1-Acetyl-2-methylcyclohexane[13] rearranged to cis-2-methylcyclohexanyl acetate which was converted to the acid phthalate and identified as such. The overall yield was 63%. trans-1-Acetyl-2-methylcyclohexane, treated in the same manner, gave a 55% yield of trans-2-methylcyclohexanyl acid phthalate. No other theoretical reaction products were found. cis and trans-1-acetyl-2-methylcyclopentane behaved similarly. The products were obtained as 3,5-dinitrobenzoates in 66% and 64% yields respectively. 3α-Acetoxy-17β-pregnan-20-one[14], which has a β-acetyl group at the 17 carbon on the steroid nucleus, rearranged with perbenzoic acid to give, on saponification, a 37% yield of 3α, 17β-etiocholandiol. No other product was found.

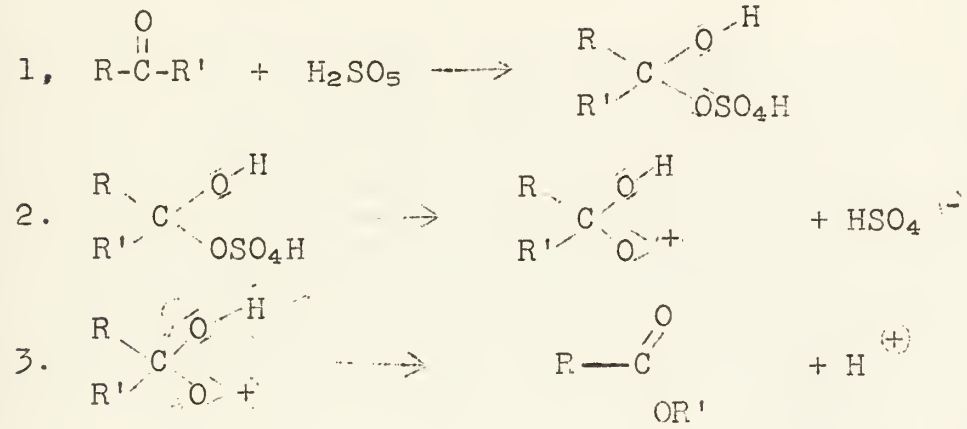


More conclusive proof of the stereospecificity of the rearrangement was demonstrated by the reaction of optically active 3-phenyl-2-butanone with perbenzoic acid[15]. Varying degrees of optical activity of the ketone gave, on removal of unreacted ketone with Girard-T reagent, optically active phenylmethylcarbinyl acetate with the same degree of asymmetry as the starting material. The configuration remained unchanged during the rearrangement. This property of the reaction was used to determine the relationship between

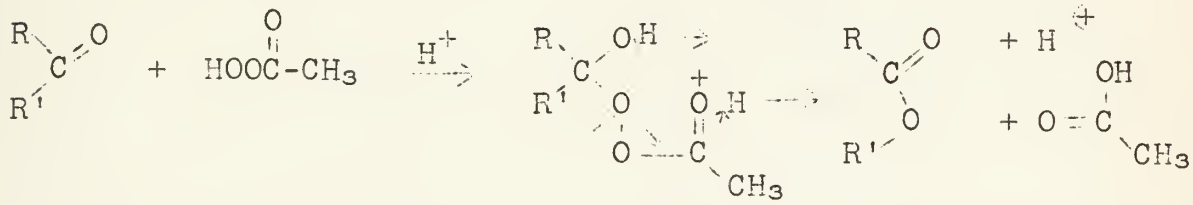
the <u>cis</u>-decahydro-2-naphthoic acids and the <u>cis</u>-2-decalols[16].



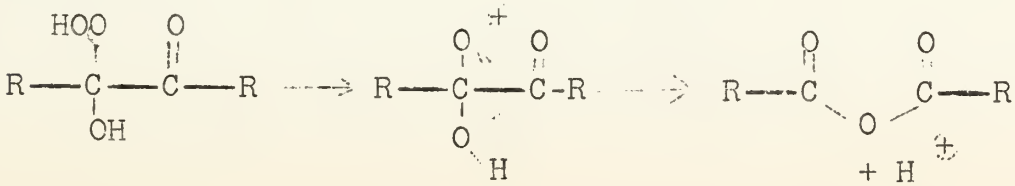
The mechanism of the reaction is believed to be ionic based on facts presented above; namely (1) the reaction is acid catalyzed; (2) as the polarity of the solvent is increased, the rate of disappearance of perbenzoic acid increases and (3) the migratory aptitudes of the groups are in accord with an ionic mechanism. Criegee[17] and Robertson and Waters[18] presented the following general mechanism involving persulfuric acid:



The main objection to this mechanism was that an intermediate in which oxygen bears a positive charge was conjectured. E. Doering postulated a concerted version of the Criegee-Waters mechanism:



Other mechanisms[6,8] were postulated in which OH^+ attacked the carbonyl oxygen to form a complex which then rearranged. These were objectionable because of unprecedented existance of the OH^+ group. A reaction difficult to explain by the above mechanisms was the cleavage of α-diketones to give anhydrides or the hydrolysis products thereof. The course of the reaction required that RC^{O}- migrated in preference to such groups of high migration aptitudes as anisyl and phenyl. Leffler[19] proposed a 'cyclic' mechanism as an explanation:



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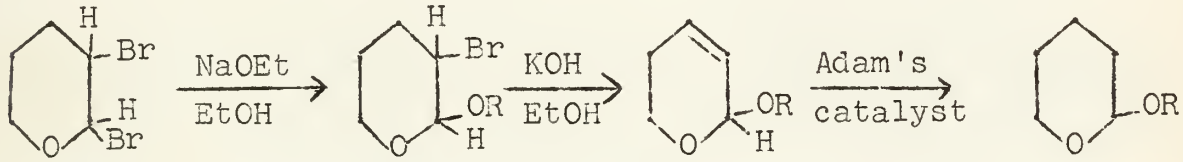
DEVELOPMENTS IN THE USES OF 2,3-DIHYDROPYRAN

Reported by Lewis I. Krimen November 20, 1953

Introduction. The earliest investigations of the reactivity of the ethylenic bond in 2,3-dihydropyran were conducted by Paul. In a series of papers[1,2,3,4,5] he described methods of preparing (1) 2,3-dibromotetrahydropyran, (2) 2-alkoxytetrahydropyrans, (3) 2-alkyltetrahydropyran, (4) 1,5-epoxy-2-bromo-1-pentene and (5) hemiacetals of 2-bromo-5-hydroxypentanal. In a later paper[6] Paul described the reaction of 2,3-dihydropyran with chlorine to give 2,3-dichlorotetrahydropyran and the subsequent preparation of 2-methoxy-3-chlorotetrahydropyran.

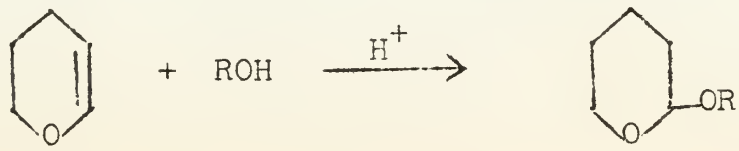
Reactions of 2,3-dibromotetrahydropyran. Woods and Sanders extended the investigations of Paul and studied the reaction of 2,3-dibromotetrahydropyran (I) with methyl and ethyl alcohols.[7] As would be expected the difference in the reactivity of the two bromine atoms of this substance was very great. Alcoholysis of the bromine atom on the carbon atom adjacent to the oxygen linkage was readily accomplished in a cold alcohol-sodium alcoholate solution or in alcohol saturated with dry ammonia. The product of this reaction was 2-alkoxy-3-bromo-tetrahydropyran (II). Under these conditions the second bromine atom was completely inert. When alcoholic potassium hydroxide was used the 2-alkoxy-3-bromo-tetrahydropyran was dehydrobrominated with the formation of the corresponding 2-alkoxy-Δ^3-dihydropyran (III). Reduction with Adam's catalyst led to 2-alkoxytetrahydropyran (IV).



I II III IV

Acid hydrolysis of IV afforded the isolation of 5-hydroxy-pentanal; acid hydrolysis of III in the presence of 2,4-dinitrophenylhydrazine led to the hydrazone of 5-hydroxy-Δ^2-pentenal. If the acid hydrolysis of III is followed by a steam distillation the semicarbazone of the expected 2,4-pentadienal can be isolated.

Formation of acetals(2-tetrahydropyranyl ethers). The acetal studies of Paul[2] led Woods and Kramer[8] to the preparation of a number of acetals from 2,3-dihydropyran according to the following equation.



The radicals used were methyl, ethyl, n-propyl, allyl, n-butyl, phenyl, benzyl and furfuryl. 2,2'-(sym-Ethylenedioxyditetrahydropyran, in which R = $-CH_2CH_2-$, was prepared in this manner using ethylene glycol.

These acetals are stable in basic media and therefore are easily isolated after destruction of the acid catalyst with a strong inorganic base. Hydrolysis of the acetals by acids in aqueous media in the presence of 2,4-dinitrophenylhydrazine yielded 5-hydroxypentanal-2,4-dinitrophenylhydrazone.

The synthesis of the bis-2-tetrahydropyranyl ethers of resorcinol, catechol and hydroquinone has also been reported.[9] To determine whether such acetals would serve as useful intermediates in synthetic work, the ethers were metalated with n-butyl lithium. Conversion of the organometallic compounds to the corresponding hydroxy acids by carbonation and subsequent acidic hydrolysis established the position at which metalation had occurred.

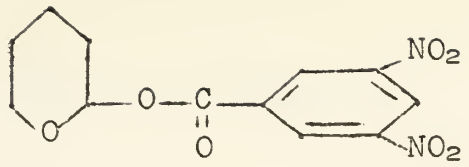
Aliphatic acetals were also prepared from trimethylene chlorohydrin, ethylene bromohydrin, and pentamethylene glycol. 2-(γ-Chloro-n-propoxy)-tetrahydropyran (I) underwent a Williamson ether synthesis to give 2-(γ-ethoxy-n-propoxy)-tetrahydropyran (II). Hydrolysis of this acetal gave the monoethyl ether of trimethylene glycol (III). This suggests a method of synthesizing mono ethers of glycols.

$$\underset{\text{I}}{ClCH_2CH_2CH_2OR} \xrightarrow{C_2H_5ONa} \underset{\text{II}}{C_2H_5\text{-}O\text{-}CH_2CH_2CH_2OR} \xrightarrow[H_2O]{H^+} \underset{\text{III}}{C_2H_5O\text{-}CH_2CH_2CH_2OH}$$

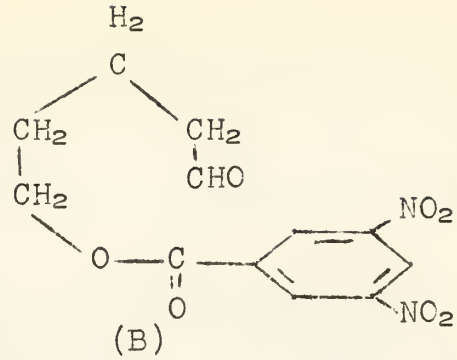
This reaction was extended to alkyl and aralkyl mercaptans to prepare the methyl, ethyl, propyl, hexyl, and benzyl thioacetals of 2,3-dihydropyran, using anhydrous hydrogen chloride as a catalyst. These acetals, which are stable to alkali and are decomposed by dilute acids, are used for flavoring and odor masking.[10]

2,3-Dihydropyran has been treated with halogen yielding compounds such as t-butyl hypochlorite and bromonitromethane in the presence of base to give 2-alkoxy-3-halotetrahydropyrans.[11] Hawkins and Bennett[12] emusified dihydropyran in water and then added chlorine to give the α-chlorohemiacetal.

Ester and Ketone Synthesis. By the addition of an excess of dihydropyran to 3,5-dinitrobenzoic acid, Woods found that an adduct was formed which was excellent for characterization. This product did not form a semicarbazone when treated with free semicarbazide in methanol; therefore structure A is preferred to structure B.[8]

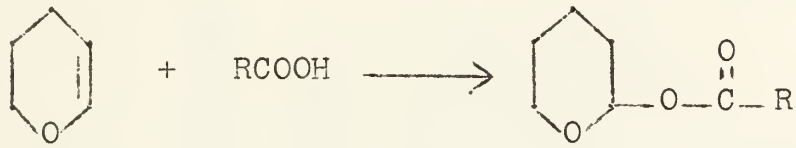


(A)



(B)

In a British patent[13] Bremner and Jones described the reaction of 2,3-dihydropyran with mono- and dibasic acids to give acyloxypyrans.



In a study of the reaction of dihydropyran with carboxylic acids it was found that in the presence of acid catalysts esterification is substantially complete at room temperature but that dissociation takes place with an increase in temperature.[14] In a more recent investigation[15] Bowman and Fordham reported a new and general synthesis of ketones from malonic acids and acid chlorides.

The ease of preparation and pyrolytic decomposition of these esters under such mild conditions offers a new method for the protection of carboxylic acid groupings and with its aid a new ketone synthesis has been evolved. The following equation illustrates the general method of preparation:

$$\underset{\text{I}}{RCH(CO_2R')_2} \xrightarrow[]{\substack{1)Na \\ 2)R''COCl}} \underset{\text{II}}{R''COCR(CO_2R')_2} \rightarrow \underset{\text{III}}{R''COCR(CO_2H)_2} \rightarrow \underset{\text{IV}}{R''\overset{O}{\overset{\|}{C}}CH_2R}$$

R'=pyranyl

Refluxing of compound (II) with a small amount of acetic acid brings about irreversible degradation of the keto-ester to ketone, carbon dioxide, and presumably dihydropyran.

This method has also been extended to β-keto-esters; ethyl 3-ketononoate was prepared from n-heptanoyl chloride and ethyl hydrogen malonate.

2-Tetrahydropyranyl ether as a protecting group. The synthesis of various steroids and other polynuclear compounds necessitates the blocking of one or more hydroxyl groups while another group is subjected to reaction. Ott and coworkers[16] reported an excellent means of protecting nonphenolic hydroxyl groups in the steroid molecule using 2,3-dihydropyran. The ease of formation and cleavage of the 2-tetrahydropyranyl ether as a protecting group and its stability toward lithium aluminum hydride and acylating conditions has afforded a most practical synthesis for testosterone acyl esters in excellent yields.

The 2-tetrahydropyranyl ether was also used as a protecting group in the preparation of 3-α-hydroxyetiocholane-17-one.[17] In order to avoid the formation of insoluble complexes Greenhalgh and coworkers protected the 3β-hydroxyl group of dehydroepiandrosterone by formation of the 2-tetrahydropyranyl ether, such adducts being stable to organometallic reagents.[18]

Following Parham's synthesis of 2,6 dihydroxybenzoic acid[9] Geissman used 2,3-dihydropyran to protect the hydroxyl groups in preparing 2-methy-7-hydroxychromone from resacetophenone.[19]

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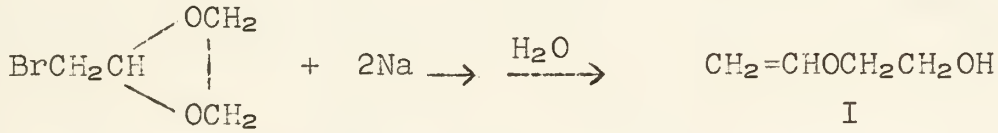
THE SYNTHESIS OF VINYL AND α,β-OLEFINIC ETHERS

Reported by Richard E. Lyle November 20, 1953

I. The Action of Metals on Halogenated Acetals.

Wislicenus[1] synthesized vinyl ethers by the action of sodium metal on a chloroacetal. Thus, he prepared ethyl vinyl ether from β-chloroethyl acetal. Hill and Pidgeon[2] adapted this method to produce ethylene glycol monovinyl ether (I) from the cyclic acetal of bromoacetaldehyde and ethylene glycol.



Halovinyl ethers were prepared by Jacobs, Cramer, and Hanson[3] who removed halogen and alkoxide from dihaloacetals by treating them with metallic zinc.

II. Dehydrohalogenation of Halogenated Ethers.

Hibbert, Perry, and Taylor[4] prepared divinyl ether from β,β'-dichlorodiethyl ether by the action of KOH and heat in a copper flask. Ruigh and Major[5] later found that ammonia gas catalyzed the reaction.

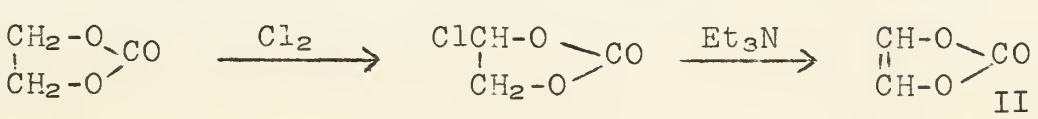
Lauer and Spielman[6] used this method in the final step of a general synthesis of substituted vinyl ethers by the following scheme:

$$RCH_2CHO + R'OH + HCl \longrightarrow RCH_2CH(OR')Cl + H_2O$$
$$RCH_2CH(OR')Cl + Br_2 \longrightarrow RCHBrCH(OR')Br + HCl$$
$$RCHBrCH(OR')Br + R''MgBr \rightarrow RCHBrCH(OR')R'' + MgBr_2$$
$$RCHBrCH(OR')R'' + KOH \longrightarrow RCH{=}C(OR')R'' + KBr + H_2O$$

Olefins may be converted to vinyl ethers through an alkoxy-iodo intermediate.[7] The olefin is treated with mercuric oxide, iodine, and the desired alcohol at -10 to -6°C to form the alkoxy-iodo compound which is then distilled with alcoholic sodium hydroxide or alkoxides giving the vinyl ether. In this manner, 2-methoxybutene-2 was prepared.

Acyl chlorides may be added to olefins giving chloro-alkoxylated compounds which may then be dehydrochlorinated with KOH.[8]

The dehydrohalogenation may be effected by amines. Hurd and Botteron[9] thus prepared ethyl vinyl ether from chloro-diethyl ether. This method has been used for the preparation of vinyl esters. Recently, Newman and Addor[10] prepared vinylene carbonate (II) in this manner.

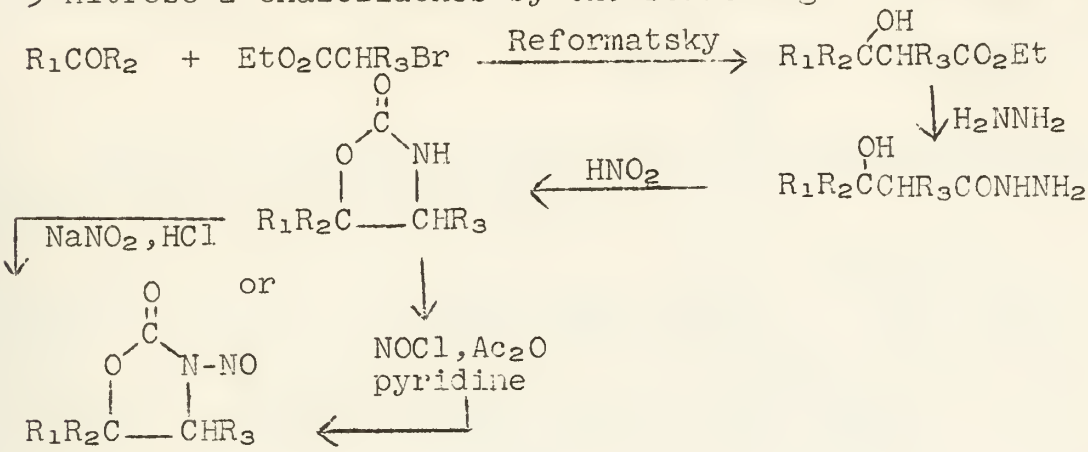


Dehydrohalogenation by heat has been reported.[11]

$$CHCl_2CHCl(OEt) \xrightarrow{\Delta} CCl_2{=}CH(OEt)$$

III. Alkaline Decomposition of 3-Nitroso-2-oxazolidones.

Newman and Kutner[12] prepared a series of substituted 3-nitroso-2-oxazolidones by the following transformations:



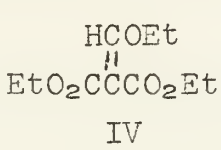
When 4,5,5-triphenyl-3-nitroso-2-oxazolidone (III, $R_1{=}R_2{=}R_3{=}\phi$) was treated with 50% potassium hydroxide in methanol, 1,2,2,-triphenylmethoxyethylene was formed. Upon treatment with sodium methoxide in absolute methanol 5,5-diethyl-3-nitroso-2-oxazolidone was converted to 2,2-diethylmethoxyethylene in 70% yield.

IV. The Action of Magnesium Compounds on Halides.

Summerbell and Bauer[13] attempted to prepare 2,3-diethyldioxane by the action of ethylmagnesium bromide on 2,3-dichlorodioxane. The product, however, was dioxene. The desired product was finally obtained by treating the Grignard reagent with zinc chloride or cadmium chloride etherate, then with the 2,3-dichlorodioxane.[14] Summerbell and Umhoefer[15] later found that a mixture of magnesium metal and magnesium iodide was a better reagent for the preparation of the dioxene.

V. Condensation of Active Methylene Compounds with an Ortho Ester.

Claisen[16] synthesized ethyl ethoxymethylene malonate (IV) from

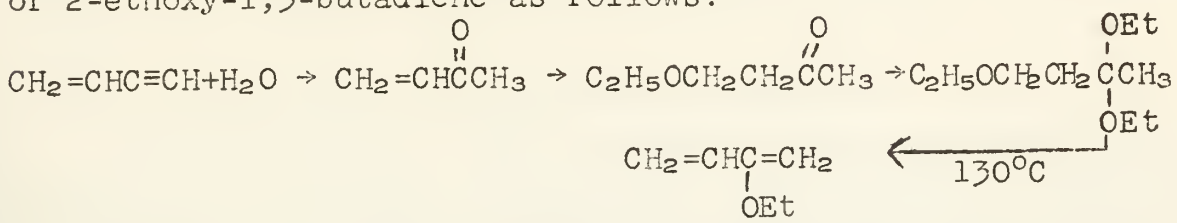


IV

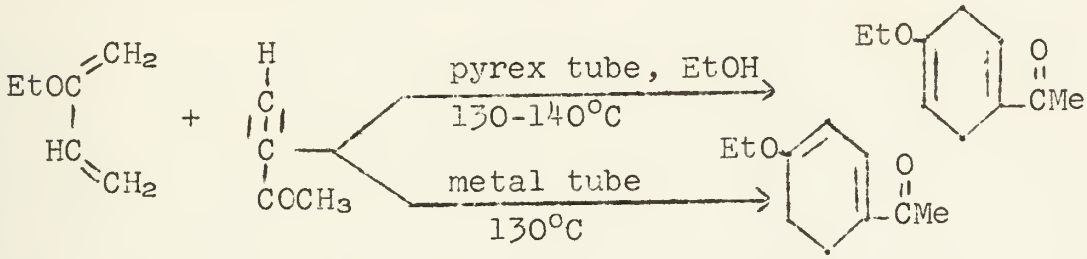
diethyl malonate and ethyl orthoformate in the presence of acetic anhydride. The reaction was later improved and was used on a large scale in the preparation of anti-malarial drugs.[17] Claisen also prepared the enol ethyl ether of ethyl acetoacetate from ethyl acetoacetate, ethyl orthoformate, and acetyl chloride.

VI. Removal of Alcohols from Ketals and Acetals.

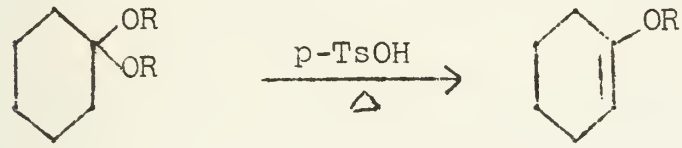
Claisen[18] found that certain ketals could be decomposed by heat to the vinyl ethers and alcohols. This method has only limited generality, but has been used in the preparation of 2-ethoxy-1,3-butadiene as follows:[19]



Braude[20] used this product in a Diels Alder reaction to obtain cyclic unsaturated ethers.



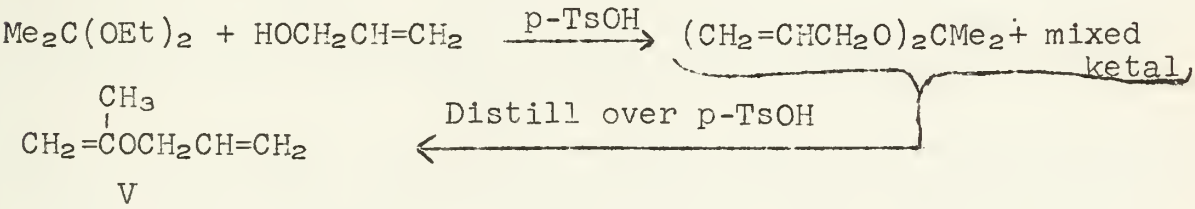
Cyclic enol ethers were obtained from cyclic ketals with para-toluenesulfonic acid as the reagent.[21]



(R = Et, n-Bu, or cyclohexyl)

Killian, Hennion, and Nieuwland[22] used p-TsOH to prepare alicyclic unsaturated ethers of low boiling alcohols, which were then converted to ethers of higher boiling alcohols by refluxing the vinyl ethers with an excess of higher boiling alcohol and distilling off the lower alcohol as it was formed.

Mixed acetals and ketals can split out the lighter of two organic alcohols to give the vinyl ether of the higher alcohol. α-Methylvinyl allyl ether (V) has been prepared in this way.[23]



Voronkov[24] prepared ethyl, propyl, butyl, isopropyl, and isobutyl vinyl ethers in good yield from the corresponding acetals by heating them with sodium bisulfate, sulfanilic acid, or aniline sulfate.

VII. The Action of Alcoholates on Vinyl Halides.

Ernst and Berndt[25] obtained vinyl ethers of phenolic substances by treating the phenolic substances with strong bases and vinyl halides. Thus, vinyl phenyl ether was obtained in

80% yield when vinyl chloride was added to a fused mixture of phenol, sodium hydroxide, and water at 180-200°C. Reppe[26] extended the reaction to a wide variety of hydroxylated organic compounds such as β-naphthol, isopropyl alcohol, diethanolamine, and glycols. Ethylidene halides were also found to give vinyl ethers upon treatment with alkoxides.

VIII. The Addition of Alcohols to Acetylene.

The formation of vinyl ethers by the addition of alcohols to acetylene has been extensively studied by Reppe[26] and is a method of considerable importance. The reaction is applicable to phenols, monohydric alcohols, multihydric alcohols, and alcohols which contain functional groups which are not sensitive to bases. The reaction is catalyzed by oxides, hydroxides, or cyanides of sodium, potassium, rubidium, or cesium, alkali zincates and alcoholates, phenolates, or naphthoates. The temperature may vary between 80 and 250°C, but best results are usually obtained in the 120-180° range. The reaction may run in either the liquid phase, usually with nitrogen to dilute the acetylene, or the vapor phase, with the alcohol vapor for the diluent. The reaction is usually run under elevated pressure, although it may be run at atmospheric pressure.

IX. The Reaction of Vinyl Acetate with Aliphatic Hydroxy Compounds.

Adelman[27] has prepared a series of vinyl ethers by an interchange reaction between vinyl acetate and an alcohol at low temperatures in the presence of mercuric sulfate. Thus, methyl glycolate vinyl ether was prepared from methyl glycolate and vinyl acetate in over 90% yield.

$$CH_3CO_2CH{=}CH_2 + CH_3O_2CCH_2OH \xrightarrow[-22^\circ C,\ 2.5\ hrs.]{HgSO_4} CH_3CO_2H + CH_3O_2CCH_2OCH{=}CH_2$$

The process was found applicable to all primary alcohols which were soluble in vinyl acetate. Secondary alcohols reacted more slowly than primary alcohols, while tertiary alcohols reacted much more slowly than the secondary alcohols. The presence of a chlorine atom in the alcohol molecule increased the rate, while the presence of a nitrile group decreased the rate. The alcohol molecule could contain a group sensitive to bases or heat. As the Reppe processes used strongly basic catalysts or zinc and cadmium salts at high temperatures, such alcohols could not be utilized in it.

The reaction is either irreversible or has an equilibrium far on the side of the vinyl ether, for when an excess of vinyl butyl ether was allowed to react with acetic acid in the presence of mercuric sulfate at -20°C, a slow steady drop in acetic acid concentration was noted, and an approximately 50% yield of higher boiling product, assumed to be 1-acetoxyethyl butyl ether was found. Unchanged vinyl butyl ether and acetic acid were recovered from the reaction mixture. Had vinyl interchange taken place, some vinyl acetate should have been found, since under the reaction conditions vinyl acetate will not react with acetic acid to form ethylidene diacetate.

Neither sulfuric acid nor mercuric acetate alone would

induce reaction. Mercuric oxide- boron trifluoride addition complex was found to catalyze the reaction, however.

Adelman proposed the following mechanism:

$$CH_2{=}CHOAc \rightleftharpoons C_2H_2 + HOAc$$

$$C_2H_2 + HgSO_4 \longrightarrow C_2H_2\text{-}HgSO_4 \text{ complex}$$

$$C_2H_2\text{-}HgSO_4 \text{ complex} + ROH \longrightarrow CH_2{=}CHOR + HgSO_4$$

This mechanism was supported by the following facts:

1. Acetylene-mercury complex salts are known and have been described.

2. Acetylene-mercury complexes and vinyl ethers have been postulated as intermediates in the reactions of acetylene with alcohols in the presence of mercuric salts to form acetals.

3. Methyl glycolate vinyl ether is formed under very mild reaction conditions, the acetal is formed with more difficulty, and the acetoxy acetal after long reaction times.

4. Acid catalyzed alcohol-ester interchange reactions do not occur readily with primary alcohols and vinyl acetate. This seems to eliminate a bimolecular acid catalyzed interchange mechanism involving acyl-oxygen fission.

5. The catalyst and conditions for alcohol- vinyl acetate reaction with acetal formation are the same as those for the direct reaction of acetylene and an alcohol to form acetals. This suggests the same intermediates in both reactions.

6. A bimolecular alkyl-oxygen fission as the primary step in the mechanism is eliminated because vinyl acetate was found not to react with dimethyl sulfate or tributyl phosphate, which can interchange at the alkyl-oxygen bond, in the presence of mercuric sulfate at reflux for long intervals.

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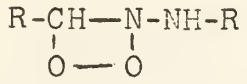
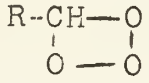
Oxidation and Autoxidation of Hydrazones

Reported by H. Ruus November 20, 1953

In 1914 M. Busch and W. Dietz[1] proposed a cyclic formulation for the autoxidation products of hydrazones (I).

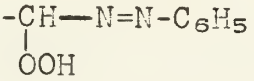
I 

They oxidized benzalphenylhydrazone, benzal-p-bromophenylhydrazone, anisalphenylhydrazone, m-nitrobenzalphenylhydrazone and other hydrazones by dissolving the hydrazone in benzene and admitting oxygen under a light pressure with shaking. In these cases the empirical formulae of the products had two more atoms of oxygen and they concluded that peroxides were formed by the addition of oxygen to the carbon-nitrogen double bond. The authors suggested the cyclic formulation of the peroxides in analogy with the structure proposed by Bach for the autoxidation products of aldehydes (II).

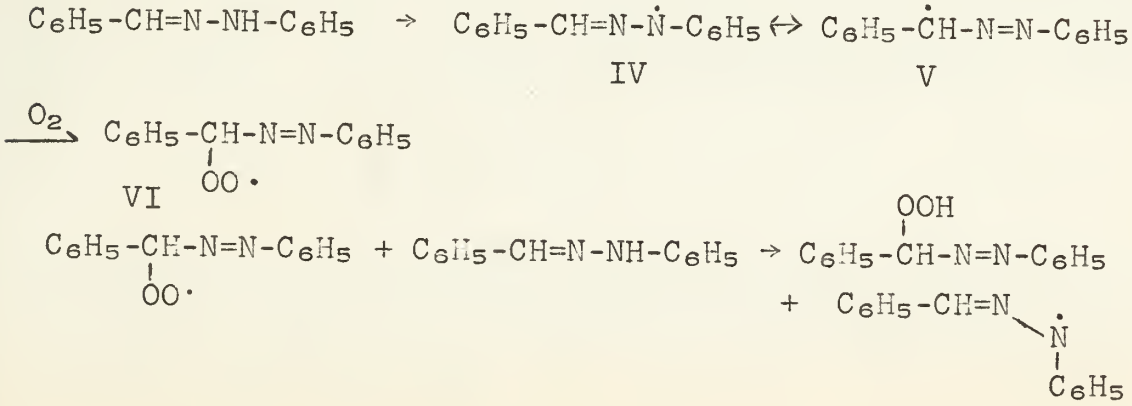
II 

The same kind of structure having the four membered ring was suggested earlier also for the peroxides of olefins.

Since the structure accepted now for the peroxides of monoolefins is a hydroperoxide, and since the color of the peroxides suggests a chromophore group, and that the presence of the four membered ring with a oxygen to oxygen and a nitrogen to oxygen bond seems improbable, K. H. Pausacker[2] in 1950 and R. Criegee and G. Lohaus[3] 1951 proposed the following structure for the peroxides of phenylhydrazones (III).

III 

The authors proposed the following mechanism for the autoxidation:



Earlier it had been found that this kind of oxidation displays the characteristics of a free-radical reaction.[4] In order that the above mechanism can function there must be a hydrogen atom on the nitrogen. To prove this Criegee and Lohaus[3] used four types of hydrazones for the oxidation experiments.

A. R-CH=N-NH-R
B. R_2C=N-NH-R
C. R-CH=N-NR_2
D. R_2C=N-NR_2

The types A and B having a hydrogen atom on nitrogen were oxidized easily when shaken in a benzene solution with oxygen under slight pressure. The types C and D having no hydrogen on nitrogen could not be oxidized under the same conditions.

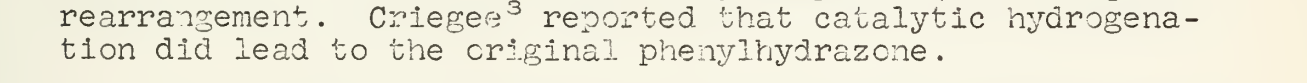
Since B. Witkop and J. B. Patrick[5] had found that the analogously constituted β-hydroperoxy-ψindoles (VII) on mild hydrogenation yielded β-hydroxy-ψindoles (VIII),

VII VIII

one would expect the hydrazone hydroperoxides to be converted to the hydroxy compounds (IX) under the same conditions.

IX

However, when such mild hydrogenation experiments were carried out with benzalphenylhydrazone hydroperoxide only benzoylphenylhydrazine was isolated (XI).

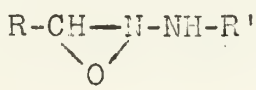


X XI

Apparently the intermediate hydroxy compound (X) undergoes rearrangement. Criegee[3] reported that catalytic hydrogenation did lead to the original phenylhydrazone.

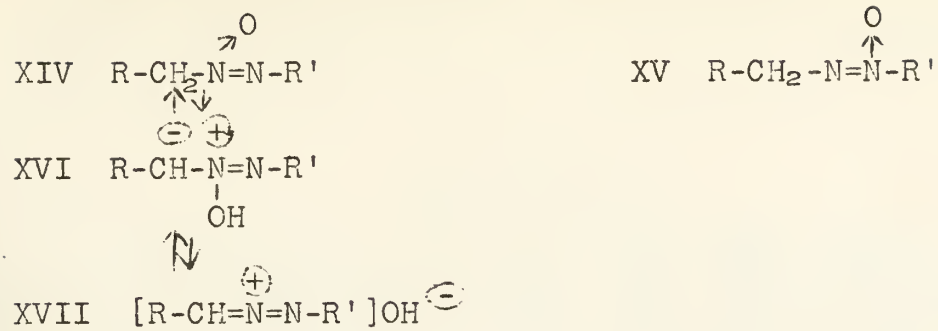
The action of peracids on aldehyde phenylhydrazones does not lead to acylated phenylhydrazones but to high-melting, neutral, salt-like, usually stable compounds containing one more oxygen[6]. For these peracid oxidation products Bergmann[6] has proposed a three-membered ring structure (XII).

XII

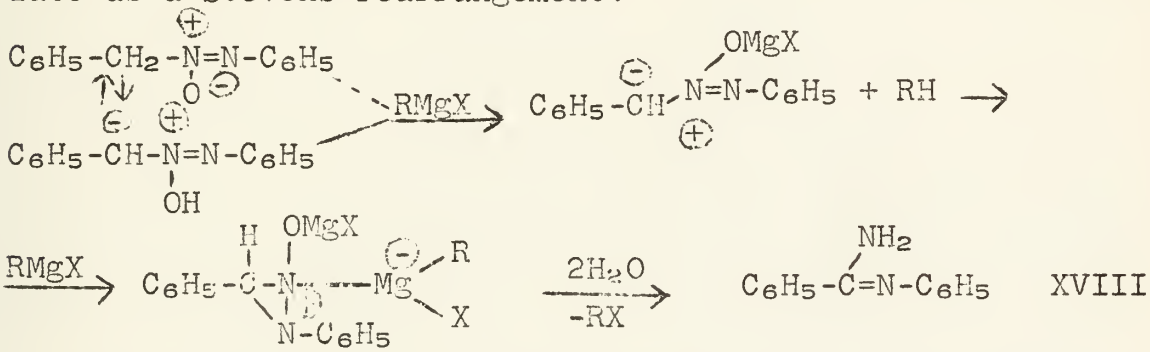


B. Witkop and H. M. Kissman[7] reinvestigated the spectrophotometric and chemical properties of these oxides derived from benzaldehyde and anisaldehyde phenylhydrazones. This led them to believe that these oxides are mixed aliphatic-aromatic azoxy compounds.

Of the two alternatives (XIV) and XV)

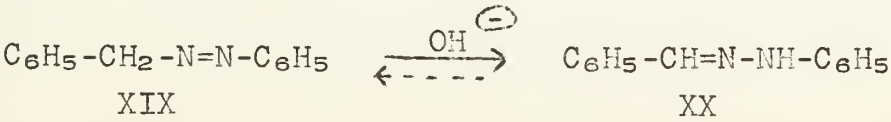


the authors prefer XIV for the following reasons: the structure XVI and the "cumulene" XVII are salt-like tautomers of XIV which helps to explain the high melting point, the stability, and the low solubility in non-polar and polar solvents. Such structures cannot be written starting with XV. The second reason is that the tautomer XVI with ethylmagnesium iodide yields phenylbenzamidine (XVIII) in at least 30% yield by a sequence of reactions which the authors formulate as a Stevens rearrangement.



The fact that no liberation of gas was observed is not explained by the first step of this mechanism. The alternative pathway starts out with the known Grignard reduction of azoxy to azo compounds, which, as the tautomeric phenylhydrazones, might undergo a cleavage to benzonitrile and aniline. However, the analogy for the easy combination of the latter fragments, under these conditions, to form an amidine is lacking.

The benzaldehyde phenylhydrazone "oxide" and its p-methoxy analog are reduced with $LiAlH_4$ to the corresponding phenylhydrazones smoothly and without indication of molecular rearrangement. This reduction involves a migration of a double bond. The intermediate benzeneazotoluene (XIX) is the first intermediate analogous to the conversion of ordinary azoxy to azo compounds by $LiAlH_4$.[8] The unstable azo compound (XIX) is apparently rearranged directly on formation in a base-catalyzed isomerization to benzalphenylhydrazone (XX).



In the catalytic hydrogenation of benzalphenylhydrazone "oxide" two different basic compounds of complex character were isolated. The reduction with aluminum amalgam gave a

non-basic compound giving a melting point depression on admixture with benzaldehyde phenylhydrazone. The ultraviolet and infrared absorption data are not in disagreement with the propose aromatic-aliphatic azoxy structure.

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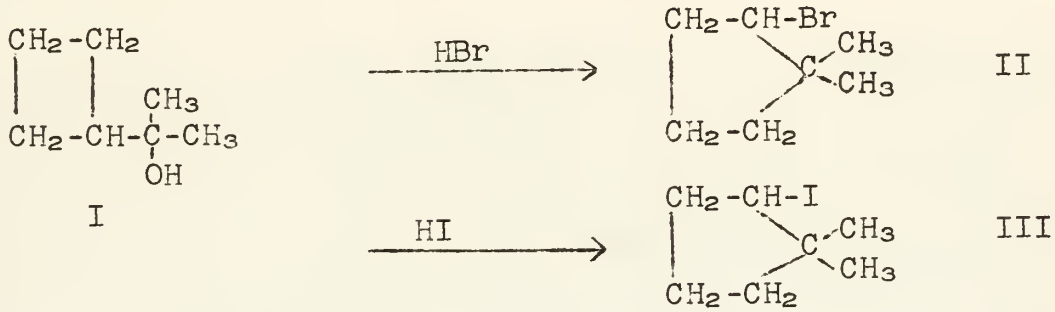
DEHYDRATION OF SOME TERTIARY CYCLOBUTYL CARBINOLS

Reported by E. W. Flynn December 4, 1953

Dehydration With Isomerization Kishner[1] in 1908 observed that the treatment of dimethylcyclobutylcarbinol (I) with hydrogen bromide and hydrogen iodide led to the isomerized products (II) and (III) respectively.

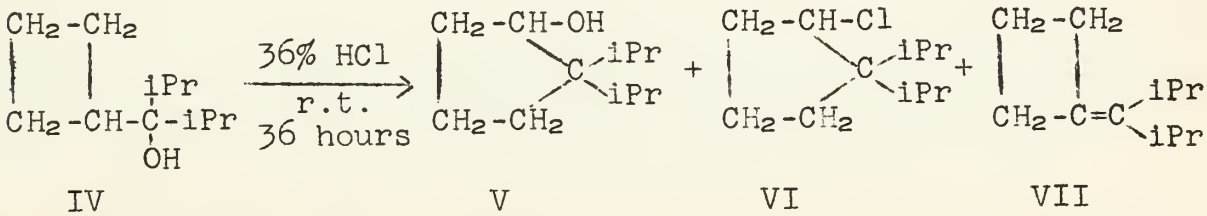


Treatment of (II) and (III) with alcoholic potassium hydroxide afforded 1,1-dimethyl-2-cyclopentene, which on oxidation gave α,α-dimethylglutaric acid.

Chavanne[2] carried out the dehydration of (I) using formic and p-toluenesulfonic acids. The products obtained were essentially the same in each case. They were characterized by their physical properties as 1,1-dimethyl-2-cyclopentene; 1,2-dimethyl-5-cyclopentene; and 1,2-dimethyl-1-cyclopentene.

In a more extensive study of dehydration reactions in which isomerization might be expected to occur Doyarenko[3] investigated the catalytic dehydration of some cyclic alcohols of the general formula $C_nH_{2n}O$, in which 'n' is equal to four and five. The reactions were carried out between 300-400° using alumina as the catalyst. The products obtained consisted of open chain and cyclic olefins as well as polymeric materials For example cyclobutylcarbinol gave a 75% yield of cyclopentene while cyclobutanol gave 1,3-butadiene.

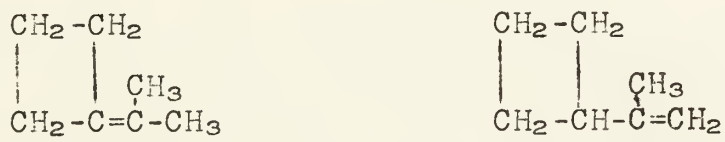
Recently Favorskaya and Yakolev[4] in a study of tertiary cyclobutylcarbinols found that diisopropylcyclobutylcarbinol (IV) on treatment with hydrochloric and sulfuric acids gave some hydrocarbon with the cyclobutyl skeleton intact as well as derivatives of cyclopentane. Reaction of (IV) with 36% hydrochloric acid for thirty-six hours at room temperature gave a mixture of the products shown below.



Treatment of (IV) with 50% sulfuric acid for six hours at 100° gave 1,1-diisopropyl-2-cyclopentanol (V) and diisopropylmethylenecyclobutane (VII) each in 8% yield.

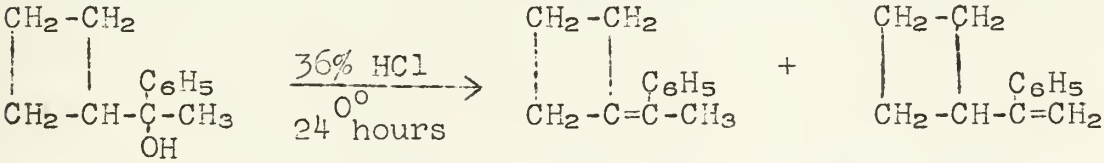
The results reported thus far are in accordance with the recognized course of a reaction that proceeds by means of a carbonium ion intermediate. Roberts and Mazur[5] have shown in an analagous case that the interconversion of the cyclopropylcarbinyl, cyclobutyl and allylcarbinyl systems is easily accomplished. They have shown further that the stability of the ions increase in the order cyclopropylcarbinyl, cyclobutyl, and allylcarbinyl. From a consideration of this fact ring enlargement and ring rupture to the open chain compound would be expected in a system in which these carbonium ions are presumed to be present.

<u>Dehydration Without Isomerization</u> In an attempt to dehydrate dimethylcyclobutylcarbinol (I) without isomerization Kazansky[6] employed the xanthate method of Chugaev. The dehydration product consisted of two unsaturated compounds. Oxidation of a mixture of these two compounds with potassium permanganate gave a series of products from which acetone and acetylcyclobutane were isolated. Catalytic hydrogenation of both unsaturated products resulted in isopropylcyclobutane. Thus he concluded that the dehydration had proceeded in two directions giving the products shown below.



This method is discussed by Alexander[7] and is general for the conversion of an alcohol, which would otherwise undergo rearrangement, to an olefin without a change in the carbon skeleton.

Favorskaya and Yakolev, in the investigation of the reactions of methylphenylcyclobutylcarbinol[8] (VIII); and ethylphenylcyclobutylcarbinol[9] (IX) with hydrochloric and sulfuric acids, found that the introduction of a phenyl group imparted stability toward ring enlargement and ring rupture. Reaction of (VIII) with 50% sulfuric acid for six hours at 100° gave a 70% yield of methylphenylmethlenecyclobutane (X). Treatment of (VIII) with 36% hydrochloric acid at 0° for twenty-four hours gave almost a 100% yield of the products shown below.

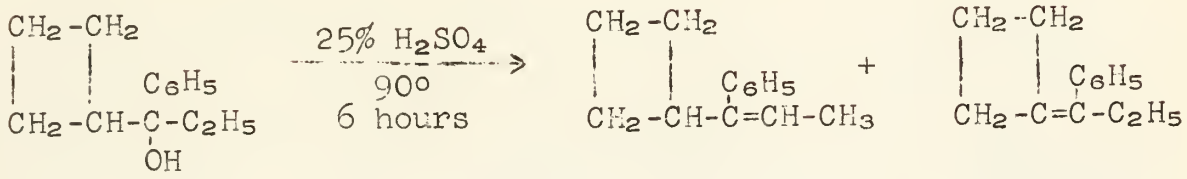


VIII X 80% XI 20%

Oxidation of (X) with potassium permanganate gave acetophenone, benzoic, succinic and formic acids. Ozonolysis of (XI) gave as the main products phenylcyclobutylketone and formic acid, with traces of acetophenone, benzoic and succinic acids.

Reaction of (IX) with 25% sulfuric acid for six hours at

90° gave the products shown below in an overall yield of 90-95%.

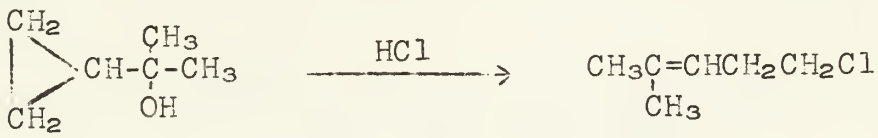


IX XII 75% XIII 25%

Oxidation of a mixture of (XII) and (XIII) with potassium permanganate gave ethylphenylketone, phenylcyclobutylketone, succinic and acetic acids. Treatment of (IX) with 37% hydrochloric acid at 0° for twelve hours and then at room temperature for six hours gave 40% of 1-methyl-2-phenyl-2-cyclobutylethylene (XII), 30% of ethylphenylmethylenecyclobutane (XIII) and 30% of a chloride (XIV) of indefinite structure. Reaction of the same alcohol (IX) with 18% hydrochloric acid at 90° after twelve hours afforded 60% of (XII), 20% of (XIII) and 20% of the same chloride (XIV).

One explanation of the apparent stability of the cyclobutyl group towards ring enlargement and ring rupture in the above reactions may be the stability of the intermediate carbonium ion. The tertiary cyclobutylcarbinyl carbonium ion which can distribute its positive charge over a phenyl group would be expected to be more stable than the secondary cyclopentyl carbonium ion that is required for ring enlargement. Also the tertiary carbonium ion containing the phenyl group would be expected to be more stable than one in which phenyl is replaced by alkyl such as (IV) which does undergo ring enlargement to some extent.

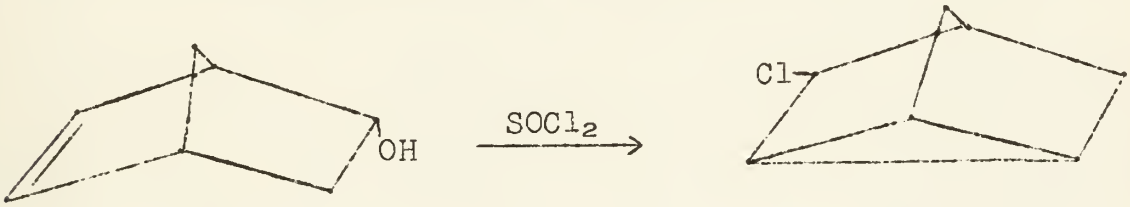
Dehydration With Ring Cleavage; and Ring Closure Analagous to the i-Steroid Rearrangement Favorskaya and co-workers at the University of Leningrad several years ago began a study of the dehydration of tertiary alicyclic carbinols. The first series of papers by Favorskaya and Fridman[10,11,12] reported the reactions of 1,1-dimethylcyclopropylcarbinol (XV); methylethylcyclopropylcarbinol (XVI); and methylphenylcyclopropylcarbinol (XVII); with hydrochloric and sulfuric acids. In the reaction with hydrochloric acid the three alcohols gave open chain derivatives, as an example that from (XV) is as follows.



XV XVIII

In addition (XVII) gave derivatives of cyclobutane. The acyclic chlorides from (XV) and (XVI) could be converted into the original cyclic alcohols on boiling with potassium carbonate, while those from (XVII) were converted into diethylenic hydrocarbons.

This conversion of the chlorides similar to (XVIII) above into structures containing a cyclopropane ring is analagous to the i-steroid rearrangement in which an ethylenic double bond participates as a neighboring group in a displacement reaction. The reaction of (XVIII) with calcium carbonate in boiling water, and with alcoholic potassium acetate and a trace of sodium iodide to give (XV) was reported earlier by Bruylants and Dewael[13]. Several examples of this type of rearrangement in cyclic systems are as follows. Roberts et et al.[14], obtained 3-nortricyclylchloride (XX) by treating endo-dehydronorborneol (XIX) with thionyl chloride.



XIX XX

Also by boiling exo-dehydronorbornylchloride with lithium carbonate in water Roberts et al.[15], obtained 3-hydroxynortricyclene. Winstein and Adams[16] have shown that the treatment of cholesteryl-p-toluenesulfonate with methanol in the presence of potassium acetate gives the i-ether.

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PERFLUOROALKYL GRIGNARD REAGENTS

Reported by Joseph E. Dunbar December 4, 1953

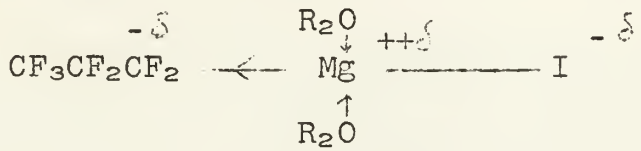
Current interest in highly fluorinated organic compounds has prompted investigators to seek convenient methods of synthesis. Perfluoroalkyl Grignard reagents have been selected as valuable intermediates in this respect and are now being studied in detail by R. N. Haszeldine.

Until recently the preparation of Grignard reagents from fluorine compounds has been achieved only with compounds containing fluorine, hydrogen, and another halogen.[1,2] Simons, Sloat and Meunier[3] in 1939 attempted unsuccessfully to prepare Grignard reagents from bromotrichloromethane and iodotrichloromethane. In 1946 Brice, Pearlson and Simons[4] observed that bromoheptafluoropropane reacted with magnesium in the presence of ether and proposed that the Grignard reagent had been formed, since addition of water to the product yielded heptafluoropropane. However, Haszeldine[5] later pointed out that this observation alone does not necessarily indicate Grignard formation, since bromofluoro-compounds can be reduced to hydrofluoro-compounds under similar conditions.

The failure of early attempts by Emeleus and Haszeldine[6,7] to prepare trifluoromethylmagnesium iodide was attributed to the increased stability of the carbon-iodine bond. At higher temperatures homolytic fission of the bond occurs, and the resulting trifluoromethyl free radical reacts with the solvent in preference to the magnesium.

In 1951 Haszeldine[8] and Henne,[9] working separately were successful in preparing perfluoroalkyl Grignard compounds. Formation of perfluorocarboxylic acids, when the reaction products were treated with carbon dioxide, was offered by both workers as proof of Grignard formation.

Perfluoroalkyl Grignard reagents must be prepared and used at abnormally low temperatures (-50° to 0°) since they are unstable. It has been found convenient to have the carbonyl compound present throughout the reaction, so that it can combine with the Grignard reagent as soon as the latter is formed.[5] The choice of solvent is also important. Since the carbon-magnesium bond in a perfluoroalkyl Grignard reagent is more ionic than in the corresponding alkyl compound, good donor solvents facilitate its formation and stabilization by formation of complexes such as

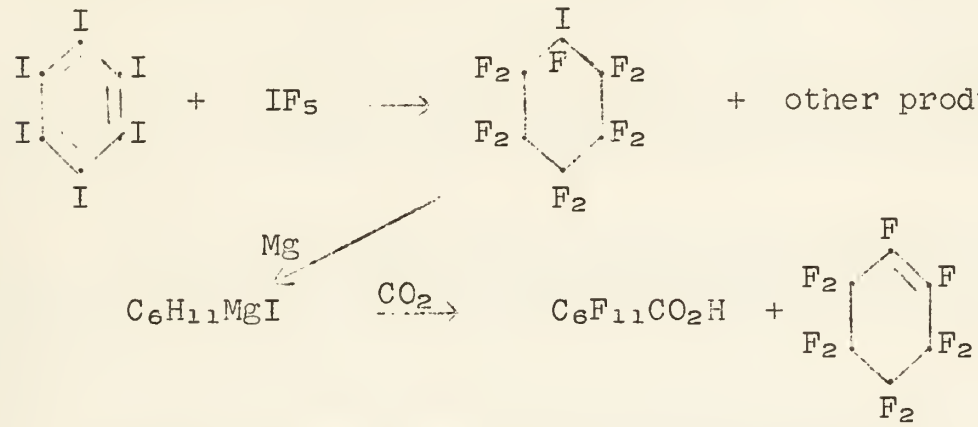


Hence, solvents such as ethyl ether, n-butyl ether, tetrahydropyran and tertiary amines have been used.

Decomposition of a Grignard reagent such as $CF_3(CF_2)_nMgI$ during its formation at other than preferred conditions or upon standing yields $CF_3(CF_2)_nH$, $CF_3(CF_2)_{n-2}CF{=}CF_2$, MgF_2, MgI_2,

and small amounts of the fluorocarbon $CF_3(CF_2)_{2n}CF_3$. Haszeldine has postulated a mechanism whereby a fluorine atom is eliminated as a fluoride ion, resulting in the formation of the olefin.[10]

The perfluoroalkyl Grignard compounds react in the normal fashion with carbon dioxide at lower temperatures. The synthesis of perfluorocyclohexylcarboxylic acid and perfluorocyclohexene has been accomplished through a Grignard intermediate:[10]



Acid chlorides do not usually give good yields of ketone when treated with excess alkylmagnesium halide because of the higher rate of reaction in the second step:

$$RCOCl + R'MgX \rightarrow RCOR' \xrightarrow{R'MgX} R(R')_2COMgX$$

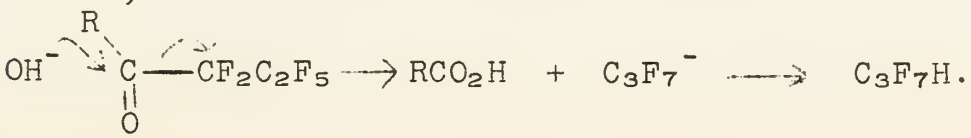
In referring to table I, we note that higher yields of the ketone are obtained when a perfluoroalkyl Grignard reagent is used, and that the ketone occurs in even higher yield when each reactant is a perfluoroalkyl compound.

TABLE I

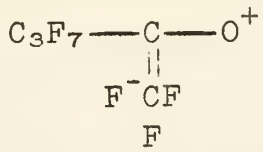
R	R'	Yield ketone (%)	Yield 3°-alcohol (%)
alkyl	alkyl	low	high
$CH_3, C_2H_5, \underline{n}\text{-}C_3H_7$	C_3F_7	15 - 20	ca 25
$CF_3, C_2F_5, \underline{n}\text{-}C_3F_7$	C_3F_7	30 - 40	ca 15

This illustrates the decreased reactivity of the carbonyl groups in the perfluoro-ketones relative to the alkylfluoroalkyl and dialkyl ketones.[11]

The ketones $C_3F_7COCH_3$, $C_3F_7COC_2H_5$ and $C_3F_7COC_3H_7$ yield heptafluoropropane when treated with dilute sodium hydroxide. It is postulated that displacement at the carbonyl group rather than addition to it is involved in the haloform reaction,



Addition to the keto group would involve the electron shift $>C=\overset{\curvearrowright}{O}$, which would be opposed by the inductive effect of the fluorine atoms on the adjacent carbon atom[11] and possibly by hyperconjugation effects[12] involving



The ease of reaction of C_3F_7MgI with a ketone R^1R^2CO decreases in the order R^1, R^2=alkyl > R^1=alkyl, R^2=perfluoroalkyl > R^1, R^2=perfluoroalkyl. This might be expected, since electronegative R groups will tend to reduce the basicity of the carbonyl oxygen atom, thus making conditions for coordination of magnesium to oxygen (electrophilic attack) less favorable.[11]

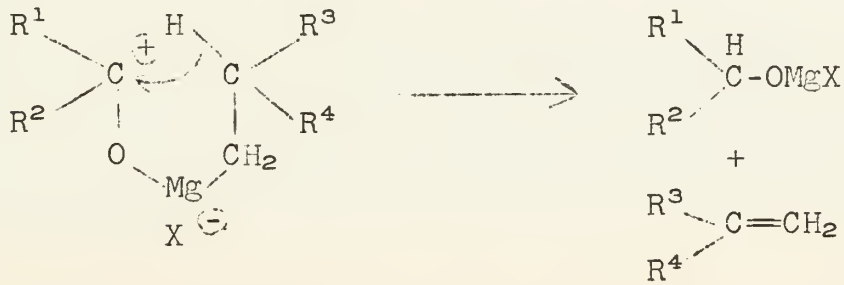
It has been shown that the percentage reduction during the reactions of fluorine-containing carbonyl compounds is higher than with the corresponding unsubstituted compounds.[11,13,14,15]

TABLE II. Reactions with Ethyl Grignard.[14]

Compound	Reduction,%	Addition,%
$CF_3CO_2CH_3$	35.0	56.0
$C_2F_5CO_2CH_3$	66.0	29.0
$C_3F_7CO_2CH_3$	68.6	12.5
CF_3COCH_3	13.9	78.9
$C_2F_5COCH_3$	44.5	41.6
$C_3F_7COCH_3$	61.6	18.0
C_3F_7CHO	61.0	19.0

It is interesting to note also that trifluoroacetaldehyde reacts with isopropyl magnesium bromide to give the trifluoroethanol in 87% yield, none of the normal addition product being produced.

The mechanism for the reduction involves the formation of a complex from the alkyl Grignard reagent and the carbonyl compound followed by internal rearrangement with hydride ion shift:[16]



In the case of the fluorinated carbonyl compounds (R^1, R^2= fluoroalkyl) the inductive effect of the fluorine atoms should provide an increased driving force for the hydride ion shift, thereby accelerating the reduction process.[14]

On treatment with heptafluoropropylmagnesium iodide the fluoroaldehydes yield 5 to 10% of the primary alcohol, and ethyl alkane- or perfluoroalkane-carboxylates yield ca 10% of the secondary alcohol. Hydride ion shift in the complex previously described cannot be used to explain these reductions, since no β-hydrogen atoms are available.

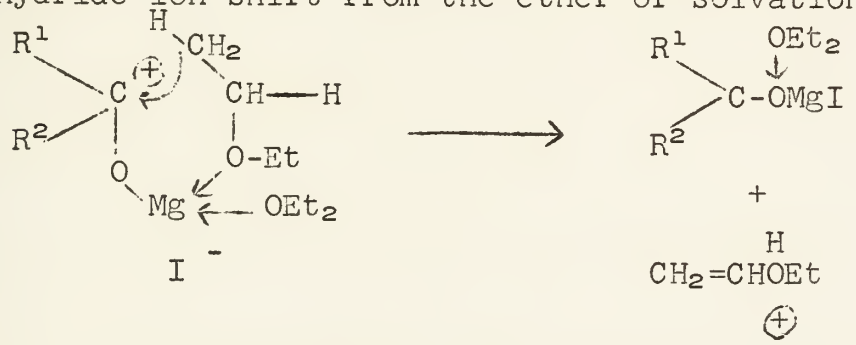
In the reactions of ethyl heptafluorobutyrate with methyl-, ethyl- or propylmagnesium iodide, and of heptafluoropropylmagnesium iodide with ethyl acetate, propionate or butyrate, the same intermediate, $C_3F_7CR(OMgI)OEt$ (R=Me, Et or Pr) is formed; but although the same reaction product, C_3F_7CHROH, is produced, the yields are markedly different (see table III).

Table III. Yield of Secondary Alcohols, %[11]

MeMgI	+	$C_3F_7CO_2Et$	0
EtMgI	+	"	62
PrMgI	+	" (predicted)	> 50
C_3F_7MgI	+	$MeCO_2Et$	8
"	+	$EtCO_2Et$	9
"	+	$PrCO_2Et$	14

Therefore, reduction occurs after the formation of C_3F_7COR.

Since the reduction involves the solvated Grignard compound, Haszeldine[11] suggests a possible mechanism, involving hydride ion shift from the ether of solvation.



It is also pointed out that such a mechanism could be tested by preparation of heptafluoropropylmagnesium iodide in a solvent having no reactive hydrogen atoms, so that no hydride ion transfer from the solvent of solvation would be possible. Attempts to prepare the Grignard reagent in perfluorotriethylamine, diperfluorobutyl ether, or benzene have so far been unsuccessful.

Although yields are frequently low in Grignard reactions involving perfluoroalkylmagnesium halides, these reactions provide routes to highly-fluorinated organic compounds which have been inaccessible by other means.

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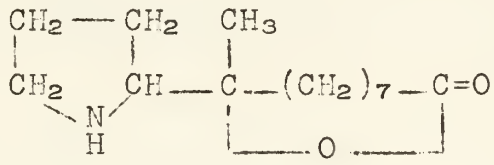
STRUCTURE OF CARPAINE

Reported by William D. Smart December 4, 1953

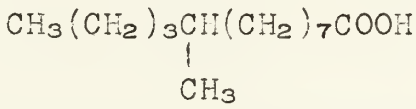
The formula of carpaine was established as $C_{14}H_{25}NO_2$ by van Rijn in 1893 and structural investigations, initiated by Barger in 1910 and continued with Robinson and co-workers[1,2], culminated in the proposal of I as the structure of carpaine.



I

Degradation of carpaine to the nitrogen-free, desoxy, fourteen-carbon acid and identification of the latter provides a key to the carbon skeleton of carpaine. Rapoport and Baldridge[3] isolated carpaine from dried papaya leaves. Then exhaustive methylations and Hofmann degradations were carried out in a manner similar to that previously reported except that the material was hydrogenated after each degradative step rather than at the end of the process.

Saponification of the degradation product gave a crystalline acid melting at 52.3 - 53.1°C. for which the formula $C_{14}H_{28}O_2$ was established by neutralization equivalent and carbon and hydrogen analysis. Recent work has demonstrated that for any group of isomeric fatty acids, the straight chain acid and the iso acid are the highest melting. Therefore, only myristic acid and isomyristic acid received serious consideration by Rapoport and Baldridge as the structure of the degradation acid. However, to remove any doubt, 9-methyltridecanoic acid (II) was synthesized, since this would be the degradation acid if the proposed structure I for carpaine were correct. The three acids and the degradation acid were



II

compared by mixed melting point determinations of the free acids, the tribromoanilides, and the p-bromoanilides. From the results, it was shown that the degradation acid was identical with myristic acid.

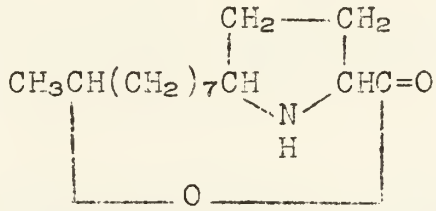
The isolation of myristic acid establishes the fact that the carbon skeleton of carpaine consists of a straight chain of fourteen carbon atoms. In view of this, the Barger-Robinson formula (I) was untenable.

Rapoport and Baldridge[4] then investigated a second structural feature of carpaine, the position of the nitrogen atom. That the nitrogen of carpaine is present as a secondary amine and in a ring had been established by the formation of typical secondary amine derivatives and the necessity of a

two-stage Hofmann degradation for its elimination. Although the N-H band was not detectable in the infrared absorption spectrum of carpaine in solution, a weak band was present at 3.0 μ when observed in an oil mull.

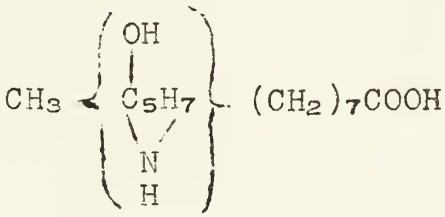
In regard to the relative position of the carboxyl group and nitrogen-containing ring, a structure such as III would be completely compatible with the previously established structural features. This possibility was easily investigated, since the amino acid resulting from lactone ring opening, carpamic acid, would be distinguishable as an α-amino acid.

III

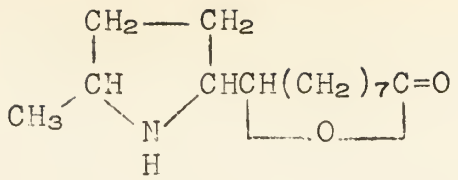


Carpamic acid was therefore subjected to the ninhydrin reaction and found to evolve no carbon dioxide, whereas proline readily evolved one mole. Further information was obtained by potentiometric titration of carpamic acid from which the pK' of the carboxyl group was found to be 4.6. Since it had been shown that, in amino acids, the pK' of the carboxyl group does not reach values of 4.5 until the amino group is beyond the γ -position, structures similar to III could be eliminated and only those formulations in which the carboxyl group and nitrogen ring are at opposite ends of the molecule were considered. If two other structural elements are incorporated, the presence of one C-CH_3 group and the oxidation of carpaine to azelaic acid, a generalized formula for carpamic acid, $C_{14}H_{27}NO_3$, may be written as in IV.

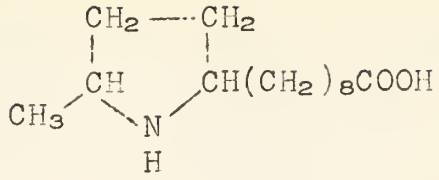
IV



Early conclusions as to the size of the nitrogen ring were based on dehydrogenations effected with selenium at 280°C. or above. The products were oils which gave positive Ehrlich tests and appeared to be substituted pyrroles. Hence a pyrrolidine nucleus was presumed to be present in the parent compound. In order to have more confidence that the dehydrogenation products reflect the structure present originally, Rapoport and Baldridge sought to find milder dehydrogenation conditions, and at the same time to establish the structure of the products. Since at this point in their investigation, V was considered to be a reasonable alternative to I as the structure of carpaine, the pyrrolidine VI was synthesized as a model compound for studying the dehydrogenation conditions.



V



VI

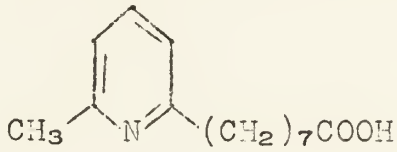
The mildest dehydrogenation conditions were found to be liquid phase dehydrogenation in boiling p-cymene with a 5% palladium-on-carbon catalyst. Under these conditions, the methyl ester of VI evolved two moles of hydrogen in three hours, after which evolution ceased completely, and the corresponding pyrrole acid was isolated after saponification in an 82% yield.

Carpaine was then subjected to these dehydrogenation conditions and found to evolve two moles of hydrogen in two hours, whereupon evolution ceased. Examination of the reaction mixture gave as the only product a water soluble hydrochloride, $C_{14}H_{21}NO_2HCl$, to which the name desoxycarpyrinic acid hydrochloride was assigned.

Since carpamic acid is $C_{14}H_{27}NO_3$, the saponified dehydrogenation product of carpaine, assuming a pyrrolidine nucleus, was expected to be $C_{14}H_{23}NO_3$. Apparently, desoxycarpyrinic acid had lost the elements of water as well. Secondly, the presence of a basic nitrogen indicated desoxycarpyrinic acid was not a substituted pyrrole. It was then shown on the basis of observed pK' values, that desoxycarpyrinic acid could be an α,α'-dialkylpyridine.

However, if desoxycarpyrinic acid were a substituted pyridine, an explanation for the origin of the third double bond must be found, since only two moles of hydrogen were evolved on dehydrogenation. Examination of the dehydrogenation reaction mixture revealed the product was present as a carboxylic acid and the saponification step, applied on the assumption that the product was a lactone, was unnecessary. Therefore, the lactone originally present in carpaine had cracked to give a carboxylic acid during the dehydrogenation, thus accounting for the third unsaturation.

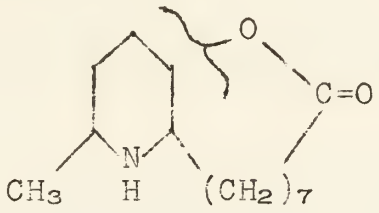
These observations then lead to the proposal of VII as the most reasonable structure for desoxycarpyrinic acid.



VII

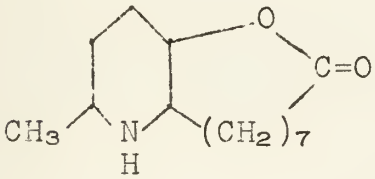
Since desoxycarpyrinic acid has been shown to contain a pyridine ring, the inference is very strong that carpaine is a substituted piperidine rather than a pyrrolidine. In order to maintain a pyrrolidine ring for carpaine, a rearrangement during the dehydrogenation reaction must be postulated. The

possible mechanisms for this have been shown by Rapoport and Baldridge[4] and by Govindachari and Narashimhan[5] to be unlikely for the reactants and products involved. Considering the above evidence at this point, the structure which best accounts for the chemistry of carpaine is VIII, with the point of attachment of the lactone ring at some undetermined position in the piperidine nucleus.

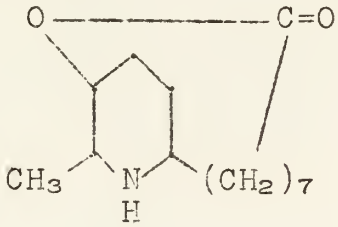


VIII

The location of the hydroxylic oxygen atom involved in lactone formation is as yet uncertain. Govindachari and Narasimhan[5] dehydrogenated ethyl carpamate to obtain a product they called ethyl carpyrinate, and demonstrated that this product was a substituted pyridine with a hydroxyl group on the 3 or 5-position of the ring. In carpaine, the point of attachment of the lactone ring to the piperidine nucleus should correspond, leading to structure IX or X for the alkaloid. Further experiments are reportedly in progress to distinguish between these possibilities.



IX



X

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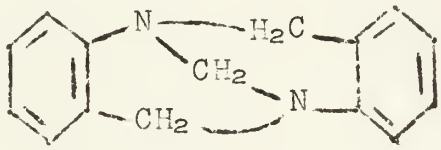
SOME EXAMPLES OF STERIC INHIBITION OF RESONANCE

Reported by Paul R. Jones December 11, 1953

Although there have been many apparently anomalous reactions that might be explained by a steric arrangement in which resonance is retarded, only in 1937 was a formal study of such a possibility begun by Birtles and Hampson[1]. In the course of the succeeding years many examples of this steric effect have been noted, in most of which nitro and amino groups are believed to be affected by neighboring methyl groups.

The steric effect being discussed here should not be confused with the classical steric effect, which is often referred to as the "ortho effect". In this latter case, the approach of an attacking reagent is believed to be blocked by the groups in the ortho positions. Steric inhibition of resonance, however, is observed when the participating groups are not coplanar. If this effect actually operates, it might be tested by subjecting the compound in question to a set of conditions in which resonance is important. The study of ultraviolet absorption is one such test; others are investigations of aromatic replacement reactions and of acid-base strengths.

A rather striking example of the use of ultraviolet is the comparison of the spectra of α-methyl-trans-stilbene and 2-phenylindene.[2] The spectra of the two are quite different although they would be expected to be almost identical from an inspection of their structures as written. The spectrum of Tröger's base shows an $E_{max.}$ between that of N,N-



Tröger's base

dimethyl-2-methylaniline and that of N,N-dimethyl-2,6-dimethylaniline[3]. The fact that the model of this base shows the angle between the planes of the ring and of the amino group to be about 45° seems to indicate that in this base a partial steric inhibition of resonance exists.

An examination of the extinction coefficients of several samples has led Remington[4] to draw certain conclusions about the effect of steric inhibition of resonance on the spectra. The two consequences of a non-coplanar arrangement which he postulates are: 1) a decrease in the extinction coefficient, and 2) an increase in the frequency at $E_{max.}$. Some data collected by Brown and Reagan[5] illustrate this trend fairly well (Table I). Remington noted that the curves of 2-nitro-N,N-dimethyl-m-5-xylidine and of dimethylaniline are very similar to each other but are different from the curve of p-nitrodimethylaniline.

	max. (Å.)	E_{max}
nitrobenzene	2520	8620
o-nitrotoluene	2500	5950
m-nitrotoluene	2565	8160
p-nitrotoluene	2640	10250
o-nitrocumene	2470	3760
p-nitrocumene	2650	10430
o-nitro-t-butylbenzene	----	----(1450 at 2500)
m-nitro-t-butylbenzene	2580	8220
p-nitro-t-butylbenzene	2650	10720
nitromesitylene	----	----(2060 at 2500)

Table I. Ultraviolet Absorption Spectra

The relative basicities of the above three compounds can be correctly predicted from the observation that the normal behavior of the nitro group in the xylidine compound is almost nullified. The relative acidities of the two compounds, (4,4',4''-trinitro)-triphenylmethane and (3,3',3'',5,5',5''-hexamethyl-4,4',4''-trinitro)-triphenylmethane, were observed by noting the relative stabilities of their sodium salts in several solvents[6]. The former proved to be much more stable, a fact which can be explained by the inhibition of the activating effect by the nitro group (through resonance) in the second compound mentioned.

In 1889 it was observed[7] that nitrosation of 5-(N,N-dimethylamino)-tetralin occurred readily while N,N-dimethyl-o-toluidine was not easily nitrosated. In the former compound the ortho group, being part of an alicyclic, six-membered ring, would not be expected to cause the amount of steric effect as would a methyl group.

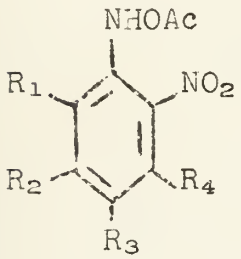
Deuterium-exchange reaction rates of aromatic compounds have been studied with the hope of shedding some light on the effect of resonance. The relationship of resonance is important here because the quinoid structure has been postulated as the group which is attacked by the deuterium cation[8]. In the series of N,N-dimethyl-o-haloanilines, the rate of exchange decreased in the order: F > Cl,Br. This study illustrates the increasing steric effect that is caused by increasing the size of the ortho substituent.

Although Friedel-Crafts reactions are not generally successful with a ring that is deactivated by a meta-directing group, at least one has been successful when the meta-directing group was sterically inhibited in its resonance with the ring[9]. The diacetyl compound was made from 2,6-dimethylacetophenone but not from 2,5-dimethylacetophenone.

Spitzer and Wheland[10] have made use of the nucleophilic displacement of sufficiently activated aromatic bromo substituents to study the effect of steric factors on resonance structures. In the examples in which the activating nitro group was unable to assume a coplanar configuration, the displacement rate was much lower. The cyano group in the same steric arrangement maintained its activating power.

In studying the deacylation reactions of certain

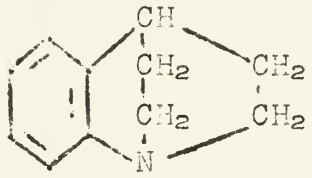
acetanilides, Wepster and Verkade[11,12,13,14,15] have recently carried out an extensive investigation of what they call "steric effects on mesomerism". The deacylation with sodium methoxide was observed to proceed only with acylanilides in which a nitro group was in the ortho or para position. The corresponding meta nitro compounds were not deacylated under the same conditions. With this limitation on the success of the reaction, the authors concluded that a mesomeric effect was necessary for deacylation to occur. The deacylation rates of a large number of compounds were studied, and the results in most instances are very convincing. In Table II some of the results are summarized.



R_1	R_2	R_3	R_4	Relative Rates
H	H	H	H	1000
CH_3	H	H	H	1
H	H	H	CH_3	10
H	H	CH_3	NO_2	1000
H	CH_3	$N(CH_3)_2$	H	500
H	H	$N(CH_3)_2$	H	63

Table II. Effect of Substituents on the Deacylation of Some o-nitroacetanilides

Benzoquinuclidine seems to be a unique compound in which resonance is, for all practical purposes, wholly absent[16]. Wepster concluded from models that the two ethylene groups form bridges above and below the plane of the N-, CH-, and the benzene ring and that the free electron pair on nitrogen is "below" the nitrogen. This means that the alkylamino



Benzoquinuclidine

group is effectively held in a rigid position that is perpendicular to the plane of the ring, a position from which there is no turning or twisting. The ultraviolet spectrum of this base was compared to that of o-t-butyl-N,N-dimethylaniline, which had been found by Remington to show considerable steric inhibition of resonance. The E_{max} of benzoquinuclidine is much smaller than that of o-t-butyl-N,N-dimethylaniline. Even more striking is the fact that the spectrum of benzoquinuclidine resembles that of tetralin. When spectra of the free amine and of the amine in 0.1 N HCl were compared, they were found to be quite similar.

The extreme stability of the colorless, crystalline amine in a CO_2-free desiccator was cited by Wepster as an indication of its inertness. Strong chemical evidence to substantiate the conclusions about the structure comes from the fact that benzoquinuclidine shows no trace of coupling with p-nitrobenzenediazonium salts, while

such sterically inhibited compounds as o-t-butyl-N,N-dimethylaniline and N,N-dimethyl-2,6-dimethylaniline give precipitates in a short time.

Wepster suggested that this unusual compound, in which the amino group is held in a firm perpendicular position without the presence of the usually troublesome classical ortho effect, affords an excellent opportunity for studying steric inhibition of resonance.

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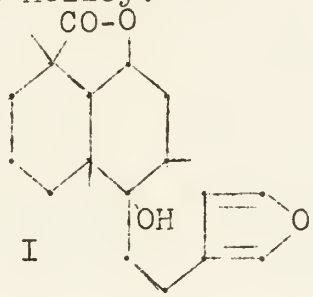
THE CONSTITUTION OF MARRUBIIN

Reported by Lester E. Coleman December 11, 1953

Introduction

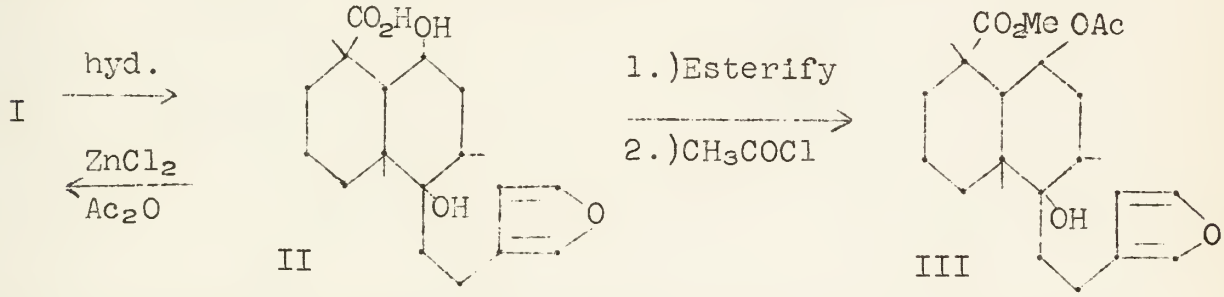
Marrubiin, $C_{20}H_{28}O_4$, is a naturally occurring diterpene and it has recently been postulated to have structure I. Marrubiin was first discovered by Mein in 1855 and its chemistry was first investigated by Harms.[1,2] Early workers did little more than test its reactions with acids, bases, and the usual classification reagents.[1-6] Postulation of structure I was the result of a compilation of recent work; a more careful study of previously published results; and excellent application of infrared and ultraviolet spectra by Cocker, Cross, Duff, Edward and Holley.[15]



I

Functional Groups

The presence of a lactone was demonstrated[7] by the hydrolysis of I to the hydroxy acid II, esterification, and preparation of the acetyl derivative III. Both II and its methyl ester could be reconverted to I.



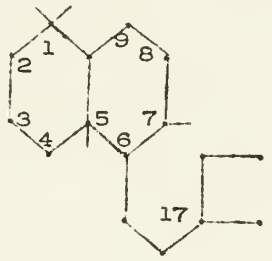
The infrared confirmed the presence of a lactone[15] and examination of the lactonic stretching frequency showed the presence of a five-membered lactone.[14] It is interesting to note that at first[17] a six-membered lactone was postulated since the infrared in Nujol gave a band at 1740 cm.$^{-1}$ which corresponds to the six-membered ring. However, in chloroform and carbon disulfide the band shifted to 1765 cm.$^{-1}$ corresponding to a five-membered ring. This lowering of the wave number in Nujol suspension has been frequently observed.[14,18] Chemical properties agree with the five-membered lactone; I gives no reaction with ammonia, aniline, or phenylhydrazine; II is lactonized by the action of diazomethane; and III must be heated quite strongly to obtain marrubiin. Infrared indicated the presence of a hydroxyl group (3440 cm.$^{-1}$) and determination of active hydrogen confirmed the presence of one hydroxyl.[8] No acetyl derivative

could be prepared and I lost a molecule of water on careful treatment with thionyl chloride or phosphorous trichloride to give triunsaturated anhydromarrubiin.[9] This indicated the presence of a tertiary hydroxyl group.

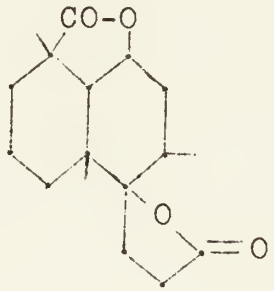
The fourth oxygen is inert[7] and there is satisfactory evidence[15] that it is present in a furan ring. Earlier oxidation studies[10] of I resulted in the loss of three carbon atoms, two double bonds, and the inert oxygen yielding a lactone $C_{17}H_{22}O_4$. A furan ring would satisfy these requirements and it has been found[15] that the ultraviolet absorption agrees with a substituted furan[13] and that the infrared of marrubiin is similar to furan and furfuryl alcohol. The presence of strong aromatic absorption bands in the 750, 1150, and 1470 cm.$^{-1}$ region of marrubiin, furan, and furfuryl alcohol and the absence of the same in tetrahydromarrubic acid and tetrahydrofurfuryl alcohol also support this postulate. However, there is no direct chemical evidence for the furan ring. There is no adduct with maleic anhydride; the ring is not hydrogenated over copper chromite; and no Shear color reaction is observed.[19] On the other hand, I does give a green color with sulfuric acid and acetic anhydride in chloroform[20] and adds hydrogen slowly over palladized charcoal. Hydrogenation over Adams' catalyst is faster and agrees with the rate expected of a furan.[9,16]

Carbon Skeleton

Dehydrogenation of I with selenium gives 1,2,5-trimethylnaphthalene (agathalene). On the basis of this evidence and by analogy with the diterpenoid alcohols, it was suggested[9] that IV was the skeletal structure.



IV

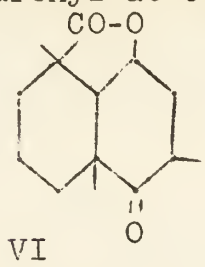


V

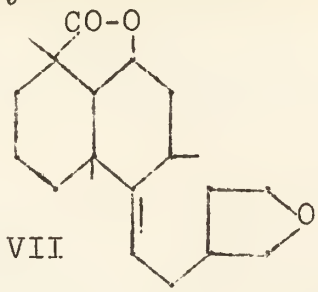
Position of Groups on Skeleton

When I is oxidized with chromic acid, the furan ring is removed yielding a dilactone. The carboxyl group left from the oxidation of the furan ring readily undergoes lactonization with the tertiary hydroxyl group which must be in the γ-position with respect to the point of attachment of the furan ring and therefore the dilactone must be V. Ozonolysis of anhydrotetrahydromarrubiin (VII) gives a keto lactone VI which is further proof of the tertiary hydroxyl group at $C_{(6)}$. In this reaction the entire $C_{(6)}$ side chain is lost. Infrared and ultraviolet indicate the presence of a ketonic group (2900A, log e=1.44) and a five-membered lactone. This keto acid gives an oxime but fails to give a semicarbazone and is not reduced by hydrogen and Adams' catalyst or under Clemmensen conditions which indicates a

hindered carbonyl. Since VI is formed by ozonolysis, anhydrotetrahydromarrubiin must be VII; the removal of the tertiary hydroxyl at $C_{(6)}$ giving rise to an exocyclic double bond.



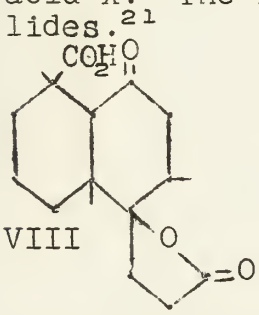
VI



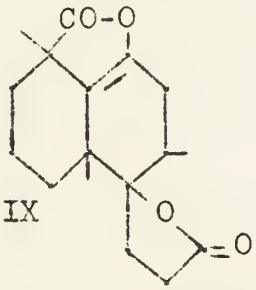
VII

Hydrolysis of the keto lactone VI gives a keto hydroxy acid which is stable in boiling water or alcohol and therefore cannot be a β-keto acid. For this reason, of the three possible positions (1,5, and 7 - assuming the carboxyl to be attached to a tertiary carbon) of attachment of the carboxyl group to the perhydronaphthalene nucleus, the 5 and 7 positions must be excluded and therefore the carboxyl group of this compound and marrubic acid must be at $C_{(1)}$. Another reason for so placing the carboxyl group is that otherwise a gem-dimethyl group would be found at $C_{(1)}$. This is not likely since improbable migrations of alkyl groups from the gem-position would be necessary to give aromatization whereas with the carboxyl at $C_{(1)}$, aromatization would take place readily with loss of carbon dioxide.

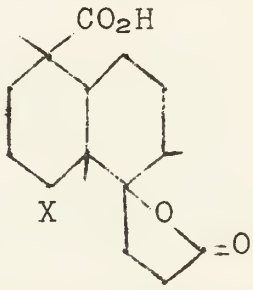
A keto lactonic acid VIII is obtained on oxidation of marrubic acid or the lactonic hydroxy acid of V with chromic acid. The presence of a five-membered lactone (1758 cm.$^{-1}$), a six-membered ring ketone (1736 cm.$^{-1}$), and a carboxyl group (1672 cm.$^{-1}$) is shown by infrared. The carboxyl group of VIII is the original group of marrubic acid. This was shown by the fact that methyl marrubate on oxidation gives a methyl ester identical to that formed by esterification of VIII. On treatment of VIII with acetic anhydride, a five-membered lactone IX is formed. Its chemical properties show that it is a βγ-butenolide; it decolorizes bromine and permanganate solutions; its solution in warm water has a pH 3-4 and after boiling ten hours in water the lactone and keto acid are present in solution in the ratio 2:1; it is completely hydrolyzed in boiling 2% aqueous methanolic HCl; it gives a keto anilide; and it is reduced over Adams' catalyst to a saturated acid X. The latter reaction is characteristic of βγ-butenolides.[21]



VIII



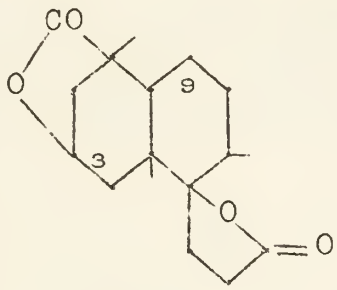
IX



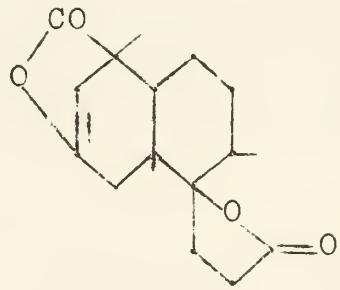
X

The βγ-butenolide shows no tendency to isomerize to the αβ-form which indicates further that the lactonic CO group is attached to a tertiary carbon atom. In deciding the formula for marrubiin, the proof that the βγ-butenolide has structure IX is necessary. A five-membered lactone of structure IV that has the lactone CO attached to $C_{(1)}$ can have its other

oxygen atom only at $C_{(3)}$ or $C_{(9)}$ as in XI and I respectively. Attachment to $C_{(3)}$ resulting in the structure XI for marrubiin is stericly possible but it would give rise to the stericly impossible butenolide XII. Therefore, the butenolide must have the structure IX (or exocyclic Δ^8 butenolide) and the corresponding keto acid the structure VIII.

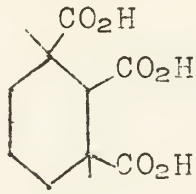


XI



XII

Further work is in progress and attempts are being made to degrade marrubiin to the tricarboxylic acid XIII. Work has also begun on the stereochemistry of the compound.



XIII

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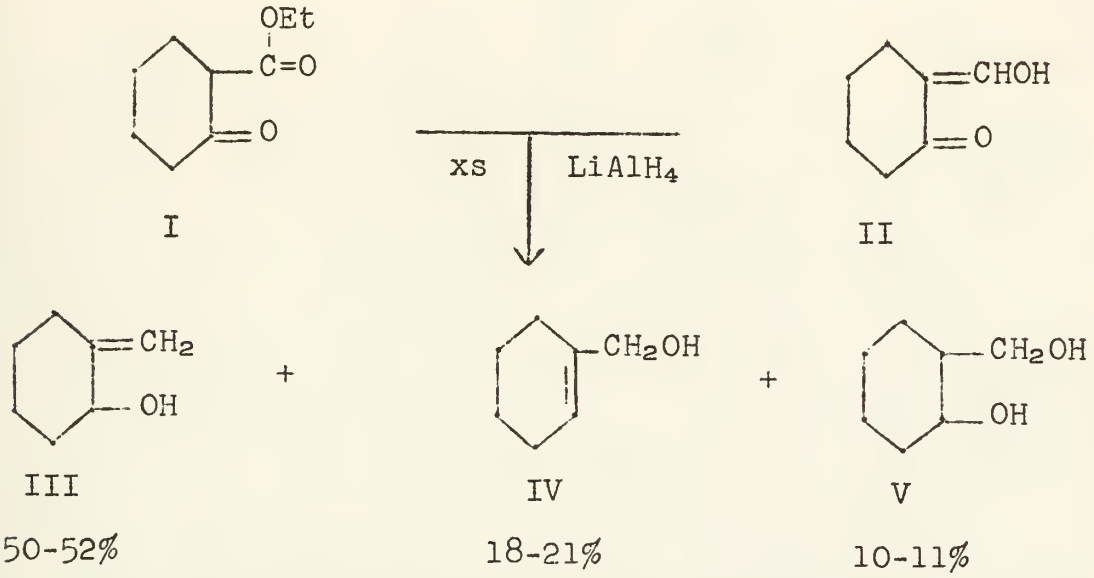
REDUCTION OF SOME ENOLIZABLE β-DICARBONYL COMPOUNDS TO UNSATURATED ALCOHOLS BY LITHIUM ALUMINUM HYDRIDE

Reported by S. A. Aspey December 11, 1953

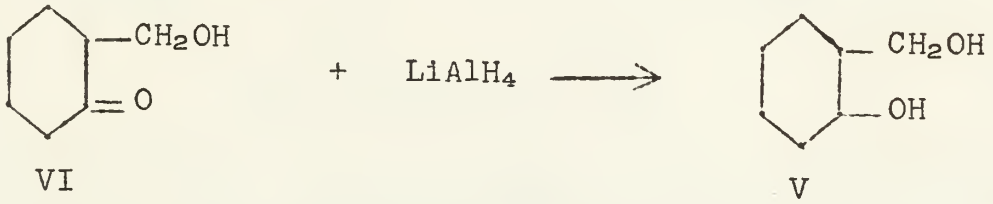
In the reduction of some β-dicarbonyl compounds with an excess of lithium aluminum hydride, Dreiding and Hartman found that the expected 1,3-glycols formed only a minor part of the reaction products.[1] The principal products (III, IV, V) were formed in approximately a 5:2:1 ratio from both (I) and (II):



A check of the literature revealed that anomalous results had been obtained in other instances of $LiAlH_4$ reduction of β-dicarbonyl compounds.[2]

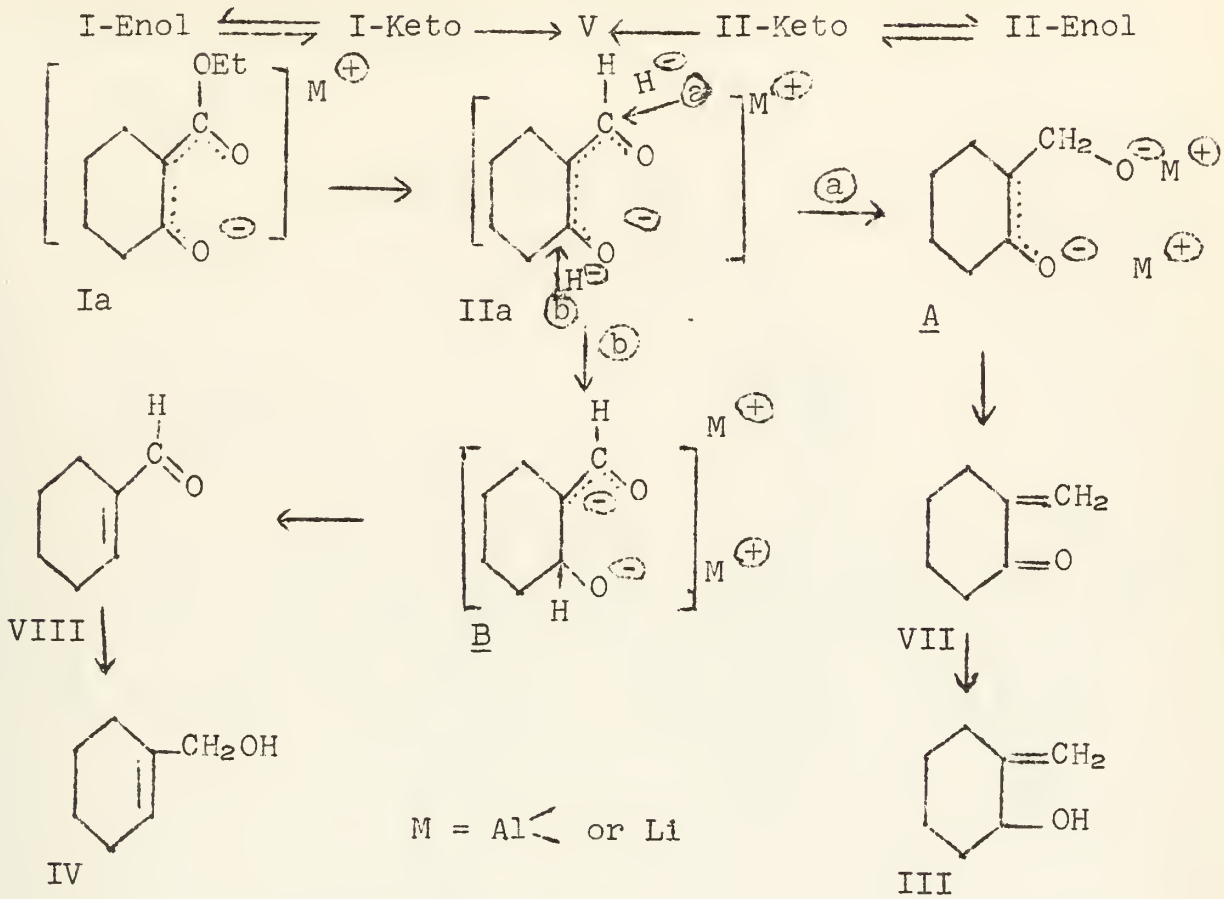
The cyclopentyl analogs of (I) and (II) were subjected to the same treatment, as a confirmatory experiment, and qualitatively analogous results were obtained.[1]

The formation of unsaturated alcohols in these reactions cannot be explained by postulating a normal reduction to the glycol and subsequent dehydration during the isolation of the products since the glycol (V) was formed in good yield under identical conditions from (VI):

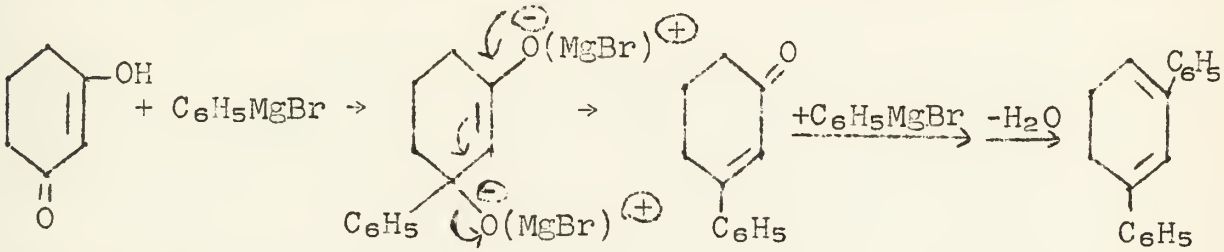


Replacement of the active hydrogen in (I) and (II) by a methyl group results in a high yield of the diol.

The following has been postulated as the course of the reaction:



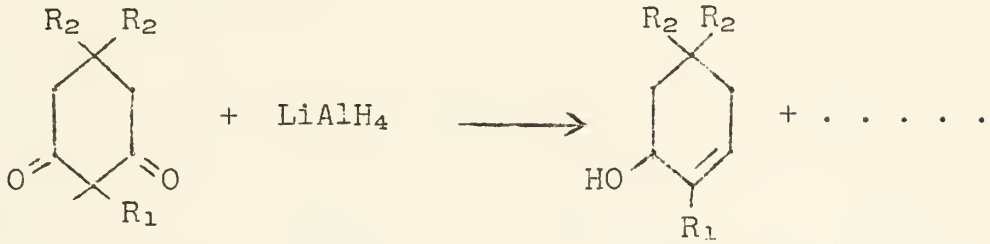
Thus, the enolized portions react with $LiAlH_4$ to form the enolate salts (Ia) and (IIa) while the non-enolic portions undergo "normal" reduction to the glycol. The ethoxy group of (Ia) is visualized as being displaced by a hydride ion to give an intermediate common to both (I) and (II) as seemingly required. Hydride attack at either (a) or (b) of (IIa) would yield the intermediate (A) or (B) respectively. The action at this point is analogous to that suggested[3] for the reaction of phenyl magnesium bromide with dihydroresorcinol, known to be strongly enolic, to yield 2,3-dihydro-m-terphenyl:



Thus (A) and (B) each lose an oxygen forming 2-methylenecyclohexanone (VII) and 1-cyclohexenealdehyde (VIII) which would then undergo further reduction to the end products in the presence of excess hydride. The formulation of the last two steps is consistent with the observation that the partial reduction of (II) yielded 20 per cent of 1-cyclohexenealdehyde (VIII) and much viscous material which may have been a dimerization product of (VII), and also with the fact that

the $LiAlH_4$ reduction of (VII) gave (III).

To check the reaction further, the investigation was extended to other types of compounds[4]:

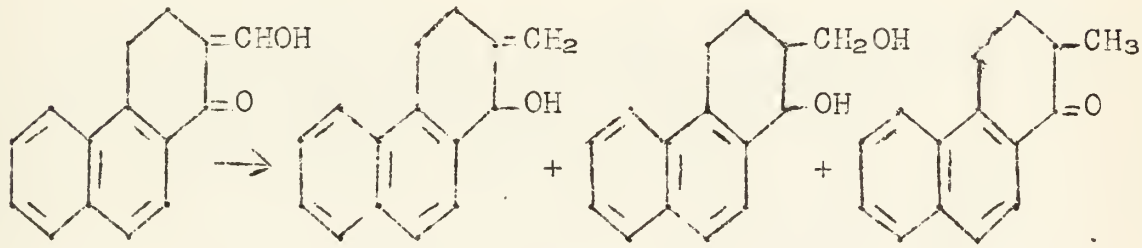
1) 

IX a,b,c

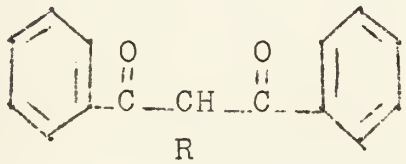
a: $R_1=R_2=H$
b: $R_1=CH_3, R_2=H$
c: $R_1=H, R_2=CH_3$

X a,b,c

Xa: 50%
b: 62%
c: 68%

2) 

54% 15% 13%

3) 

XI a,b

a: $R=CH_3$
b: $R=H$

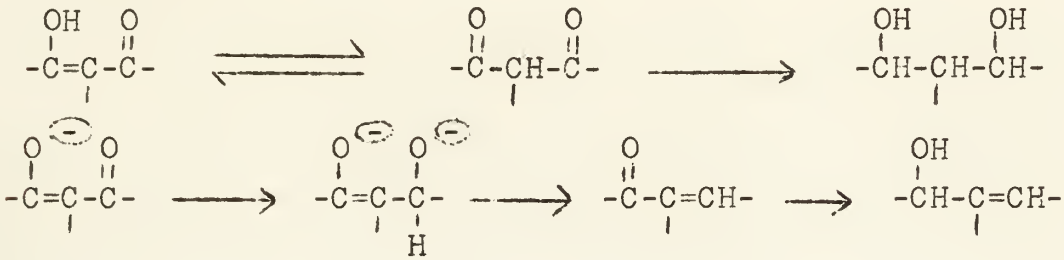
For reaction 3) above, reduction of the diketo form of dibenzoylethane afforded a quantitative yield of the glycol while the enol form (as a copper salt) was reduced under idential conditions to give 79 per cent of the unsaturated alcohol (XIIa):

XIa XIIa

The lower homolog, dibenzoylmethane (XIb) which exists almost completely in the enol form also suffered the loss of an oxygen to give a monohydric alcohol. In this case, however, the double bond was also reduced for an 83 per cent yield of 1,3-diphenylpropanol-1. This result is not inconsistent with the view that chalcone or benzalacetophenone is an intermediate since Rondestvedt[5] has found that a number of

chalcones are reduced to hydrochalcols by $LiAlH_4$. Also, cinnamyl alcohol may be reduced with the same reagent.

The mechanism of these reductions then, in summary, is suggested as:



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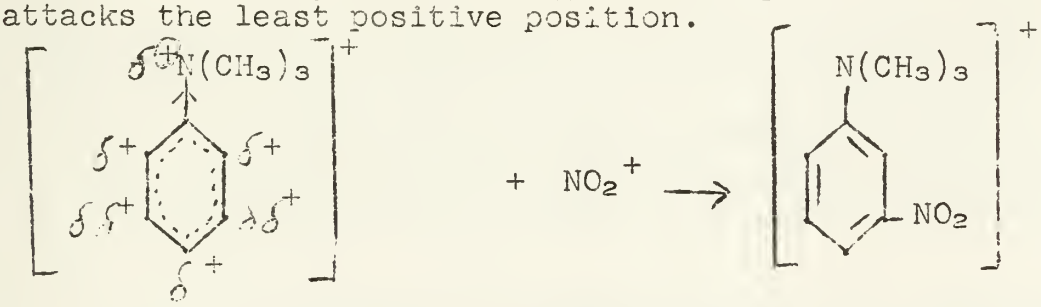
TRANSMISSION OF ELECTRICAL EFFECTS IN SATURATED SYSTEMS

Reported by Richard A. Sneen December 18, 1953

The total electrical effect of substituents on the course of organic reactions is generally regarded as being due to three separate effects operative in the ground and transition states: (1) the effect predicted by the resonance method, (2) the direct electrostatic (or field) effect, and (3) the inductive effect. The last effect is the least clearly definable one, and, indeed, may be embraced by an extension of the resonance method on the one hand, by considering that there is a polarization of the σ-bonding electrons in a chain from one atom to the next, or by a combination of these two with the field effect. The electron-withdrawing power of the m-nitro group in aromatic compounds is a commonly cited example of the inductive effect.

The mechanism of the transmission of the inductive effect in aromatic systems has not been established. It might be considered to travel through the σ - or the π -bond electrons. If the π -electrons are involved one would expect that the ortho and para positions would be affected to a greater extent than the meta position.[1] If the π -electrons are not appreciably involved in the "inductive" transmission, the question arises as to whether the σ-bonds of the ring transmit the electrical effect or whether the experimental facts can be more readily explained by assuming a classical electrostatic effect through space and solvent (the field effect), or a combination of both these effects.

The English schools of Robinson[2] and Ingold[3,4] have adopted the view that the electrical effects in aromatic systems are transmitted through the π -electrons and have invoked this theory to explain the meta orientation in anilinium ions; here the ortho and para positions are depleted of electrons and the meta position remains relatively unchanged. A positive moiety such as NO_2^+, according to their theory, attacks the least positive position.

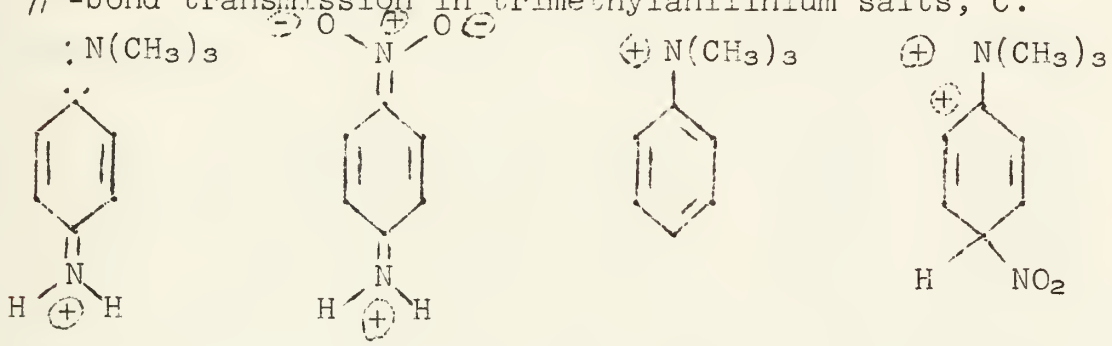


However, in principle this argument is fallacious, for it neglects a consideration of the relative stabilities of the transition states.

Furthermore, Roberts[5] has shown that their assumed electron distribution for the ground state of trimethylanilinium salts is incorrect. His experimental method used deductions based on the Hammett equation:[6]

$$\log k(K) - \log k_0(K_0) = \sigma \rho$$

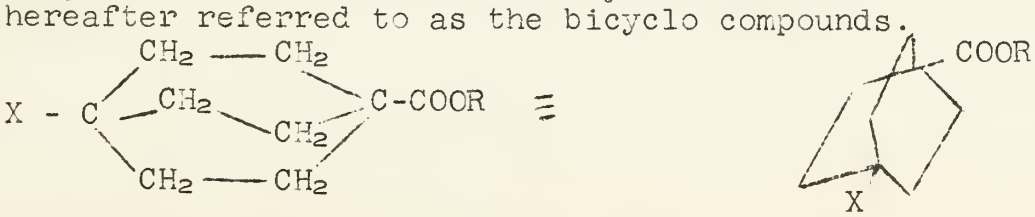
ρ is a constant characteristic of the reaction and σ is a constant characteristic of the substituent group. He has calculated the σ -values of the trimethylammonium group for several reactions, such as the ionization of benzoic acids and the ionization of anilinium salts, and has observed that the σ -values, which ordinarily are quite constant from one reaction to another, show a larger variation than is usually observed. He postulates that this is due to the large solvation effects which would be expected to be more important where the reactions being compared involve transition states differing in total charge. It is significant that the (σ meta - σ para) values remain quite constant, ranging from +0.02 to +0.21. Since ρ in all cases studied is positive, a positive value of (σ meta - σ para) implies that the <u>electrical effect of the trimethylammonium group is greater when it is a substituent at the meta position than at the para position</u>, which indicates that the most important effect is one which decreases with distance. However, the possibility still exists of a powerful "alternating" inductive effect, masked by a more powerful direct coulombic effect. This possibility can be ruled out by noting the relatively small value of [(σ meta - σ para) benzoic acid - (σ meta - σ para) aniline], +0.04, which implies that resonance of type A is not important in p-aminophenyltrimethylammonium compounds in the manner that forms of type B are important in p-nitroaniline. Hence, it seems unlikely that induction proceeds to any considerable extent by π -bond transmission in trimethylanilinium salts, C.



A B C D

Roberts has rationalized the occurrence of <u>meta</u> substitution, using the nitration reaction, by postulating that the transition state for <u>para</u> substitution is a hybrid of only two important canonical forms whereas the <u>meta</u> transition state is a hybrid of three important canonical forms. The third form, in the case of <u>para</u> substitution, has been rejected because of the position of the two positive charges on two adjacent carbon atoms (D).

Recently, Roberts[7] prepared a series of 4-substituted-bicyclo [2.2.2]-octane-1-carboxylic acids and esters (E), hereafter referred to as the bicyclo compounds.



E

These compounds were studied in order to determine the relative importance of σ-bond transmission and electrostatic field effects.[3] Their reactivities were measured in three rather distinct processes, each of which had been used previously with benzoic acid derivatives: the ionization constants, K_A of the acids in 50% ethanol (by volume) at 25.0°; the rates of reaction of the acids with diphenyldiazomethane in absolute ethanol at 30.0°; and the rates of hydrolysis of the ethyl esters in 87.33% ethanol at 30°. Variations of the substituent group X has a substantial influence on the reactivity of the bicyclo compounds. E.g., substitution of a cyano group for hydrogen increases the rate of ester hydrolysi by a factor of twenty.

In order to derive σ-values for the bicyclo series, the ρ-value for a single reaction in this series, the ionizatior of the acids, was set equal to the ρ-value for the same reaction in the aromatic series under standard conditions (50% ethanol at 25°). For the bicyclo series the Hammett equation will be altered to read:

$$\log k(K) - \log k_o(K_o) = \sigma' \rho'$$

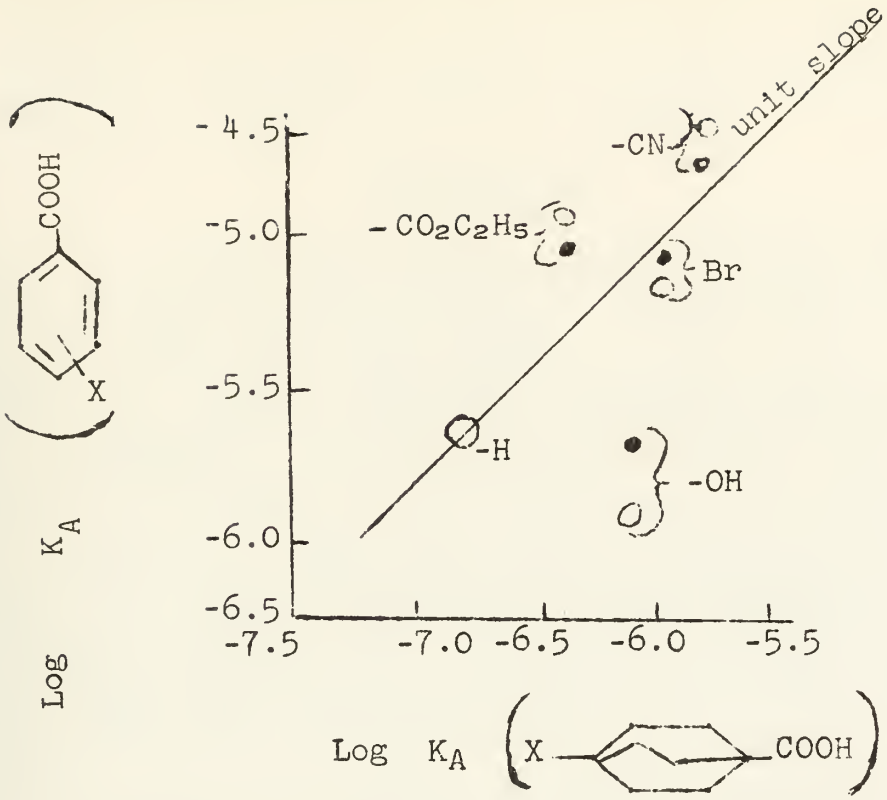
Table I

Comparison of σ'- and σ-values

Substituent	σ'	σ para	σ meta	[σ para $-\sigma'$]	[σ meta $-\sigma'$]
H	0.000	0.000	0.000	.....	.....
OH	+0.283	-0.341	+0.014	-0.624	-0.269
$COOC_2H_5$	+0.297	+0.402	+0.334	+0.105	+0.037
Br	+0.454	+0.232	+0.391	-0.222	-0.063
CN	+0.579	+0.656	+0.608	+0.077	+0.029

It will be noticed that the general trend of the variations of σ meta and σ para values parallels that of the σ' values. In every case larger variations are found in the [σ para $-\sigma'$] than in the [σ meta $-\sigma'$] values, a fact which would be anticipated, since the resonance method predicts a stronger para activation.

The comparison is strikingly shown by plotting the logs of the equilibrium (or rate) constants of the two series against one another as shown below. The graph of the ionization constants is typical. A straight line of unit slope drawn through the point for the unsubstituted compound reproduces the general trend of the reactivities.



Relationship between apparent ionization constants of 4-substituted bicyclo [2.2.2]-octane-1-carboxylic acids and m- and p-substituted benzoic acids: ● , m-benzene substituent; ○ , p-benzene substituent

A comparison of the σ'- and σ-values shows that for the <u>meta</u> directing groups ($-COOC_2H_5$, -CN) both the <u>meta</u> and <u>para</u> constants are more positive than the σ'-values; for <u>ortho-para</u> directing groups (-Br, -OH) the σ'-values are more positive. Graphically this is shown by the fact that the <u>meta</u> directing groups fall above the straight line and the <u>ortho-para</u> directing groups below. It will also be seen that the <u>meta</u> substituted derivatives lie closer to the line.

The $\sigma - \sigma'$ values should be a reasonable measure of resonance effects. Again it will be noticed that these values are positive or negative depending on whether the substituent is electron-supplying or electron-withdrawing. It thus seems reasonable to conclude that there is no need and, indeed, no justification for assuming any significant transmission of electrical effects in aromatic systems through the π-bond electrons.

Using an equation developed by Kirkwood and Westheimer, Roberts[8] has shown that a fairly good approximation to the Δ pK values of the bicyclo acids can be obtained by assuming a purely electrostatic transmission, without the necessity of postulating any appreciable σ-bond transmission. The Δ pK values represent the difference between the pK values of the

substituted and unsubstituted bicyclo acids. At present, however, there seems no very good way to calculate the contribution of the σ-bonding electrons to the total transmission of electrical effects from one end of the bicyclo ring system to the other. Thus the question of the importance of these two effects cannot yet be decided.

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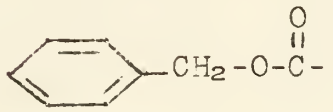
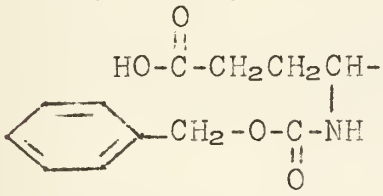
Blocking Groups and Cleavage Reagents in the Synthesis of Peptides

Reported by Richard J. Hess December 18, 1953

One of the more important blocking groups is the carbobenzyloxy group (I). Bergmann[1], who first announced its use in the preparation of polypeptides, used this group in the preparation of d-glutamyl-d-glutamic acid. His first step in the synthesis was the preparation of carbobenzyloxy chloride from benzyl alcohol and phosgene. The acid chloride was then treated with an amino acid in the presence of alkali to give in this case, carbobenzyloxy-d-glutamic acid (II). This was converted to the anhydride which reacted with glutamic acid to give the carbobenzyloxy dipeptide which was hydrogenated catalytically to d-glutamyl-d-glutamic acid (III).



(I)



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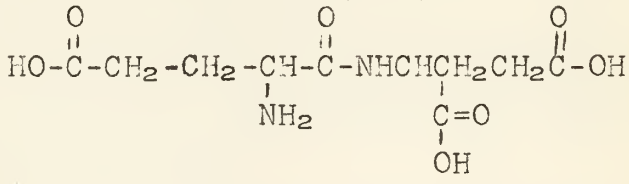
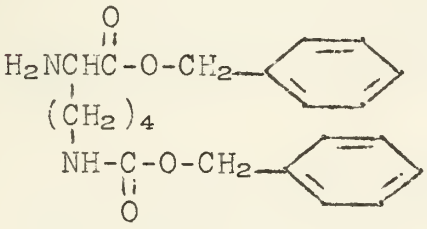


(III)

However, hydrogenation is not the only method of removing this blocking group, since 100% cleavage can be obtained by the use of phosphonium iodide in glacial acetic acid solution[2], by sodium in liquid ammonia[3], or by the halogen acids in glacial acetic acid[4]. One reagent which cleaves other blocking groups but which does not cleave the carbobenzyloxy group is HCl in methanol[4,5].

The formyl group is a moderately recent but very effective blocking group. While this group is not cleaved by catalytic hydrogenation, it can be cleaved by HCl in methanol, although benzyl alcohol is preferred. Waley[5], prepared l-tyrosyl-l-lysine using the formyl protecting group. He first prepared N-formyl-tyrosine by adding acetic anhydride to a solution of tyrosine in formic acid. This was acetylated and condensed with N-ε-carbo-benzyloxy-l-lysine benzyl ester (IV) to give o-acetyl-N-formyl-l-tyrosyl-ε-carbo-benzyloxy-l-lysine benzyl ester V. This was deformylated by HCl in benzyl alcohol and then reduced by catalytic hydrogenation to the product l-tyrosyl-l-lysine.



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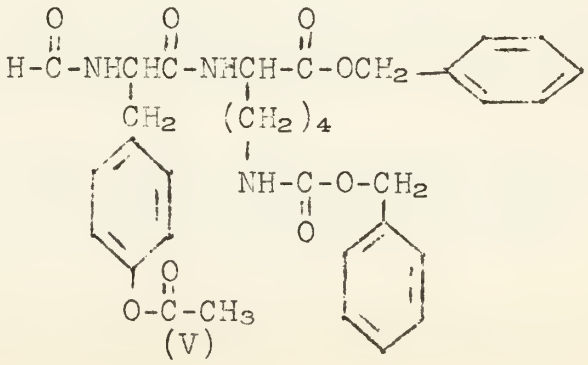
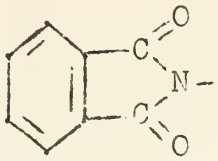


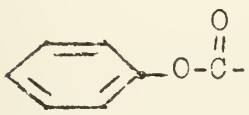
(V)

A third group of importance is the N-phthalyl group (VI)[6]. Sheenan and Frank[7] prepared dipeptides by condensing phthalic anhydride with an amino acid followed by treatment with PCl_3 to make the acid chloride. This in turn reacted with another amino acid to form an N-phthalyl dipeptide. Hydrazine was used to cleave the protecting group giving the dipeptide and phthalhydrazide The N-phthalyl group is not affected by the standard cleavage reagents but it is effectively cleaved by hydrazine or phenylhydrazine.



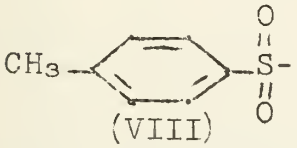
(VI)

Similar to the carbobenzyloxy group, the carbophenyloxy group (VII) differs from the former in that effective cleavage occurs only with catalytic hydrogenation or sodium in liquid ammonia[4]. Although complete cleavage of the protecting group can be brought about by using strenuous conditions with the halogen acids in glacial acetic acid, such cleavage is not desirable since it is accompanied by the destruction of the peptide linkage of the product. With the exception of cleavage reagents, the carbophenyloxy group is prepared and used in the same manner as the carbobenzyloxy group.



(VII)

Another characteristic group, is the tosyl group (VIII). Fischer and Lipschitz[8] suggested the use of p-toluene sulfonyl chloride for reactions similar to those of carbobenzyloxy chloride. The tosyl group is removed by the use of sodium in liquid ammonia without affecting the peptide linkages. While the group is also removed by the use of phosphonium iodide in glacial acetic acid, it is not preferred because of the extensive destruction of the peptide linkage which occurs as a result of the strenuous conditions necessary for cleavage[4].



(VIII)

The groups carboallyloxy and carbo-p-chlorobenzyloxy are very similar to the carbobenzyloxy group both in their preparation and their cleavage. However, the carbobenzyloxy group is preferred because it is completely cleaved under gentler conditions than either of the other two. The carboallyloxy group has the added disadvantage that frequently the allyl function is reduced during catalytic hydrogenation to the non-cleavable propyl group with a subsequent lowering of the yield of dipeptide.

Similar to the carbophenyloxy group, the carbo-p-tolyloxy group is inferior because it is harder to remove by catalytic hydrogenation and results in some hydrogenation of the peptide components.

Although there are a large number of possible groups for blocking the amino function, the previously listed groups are preferred because of their ease of cleavage or their selectivity with regard to a cleavage reagent.

Since some reagents are more reactive with regard to cleavage of certain groups, a comparison of the principle

cleavage reagents would seem desirable.

In the case of catalytic hydrogenation, it has been determined by using mixtures of peptides having blocked amino functions that the groups carbobenzyloxy and carbo-p-chlorobenzyloxy are so similar in their reactions that it is not possible to cleave one without cleaving the other. The carboallyloxy group is also a member of this series, but since it is subject to the reduction of the allyl group, it is not used normally[9]. Carbophenyloxy and carbo-p-tolyloxy do not cleave as readily as the previous groups, but their ease of cleavage would prevent them from being used in syntheses requiring selective removal of the blocking groups. Also, they require a greater period of contact than the previously listed groups and therefore are not desirable because of the partial hydrogenation of some of the peptides formed.

Although sodium in liquid ammonia will not remove the formyl or N-phthalyl groups, it effectively removes all of those groups which can be removed by catalytic hydrogenation as well as the tosyl group which is not affected by catalytic hydrogenation[10].

Phosphonium iodide (PH_4I) in glacial acetic acid is another very effective cleavage reagent which is very similar to hydroiodic acid as a cleavage agent. In fact, it reacts only when hot and then it apparently partially decomposes to HI. The tosyl group is cleaved more readily by phosphonium iodide than it is by HI, possibly due to a reduction which accompanies the cleavage. This increased rate of cleavage occurs only at higher temperatures where the peptide linkages are also attacked at a relatively high rate. Thus the use of phosphonium iodide for removal of the tosyl group is not recommended[4].

The halogen acids in glacial acetic acid are almost equally effective in removing blocking groups. It has been found that at equal molarities, the acid which is the most highly dissociated is also the most highly active in cleavage. However, HCl has the limitation that its solubility in glacial acetic acid prevents working at a concentration greater than 0.4 molar. Since HBr is more stable than HI, it is preferred as a cleavage reagent. The cleavage seems to be more rapid than cleavage occurring in aqueous solutions indicating that the absence of water is no impediment to the removal of the blocking group. The use of halogen acids in glacial acetic acid is probably the best method for removing the carbobenzyloxy blocking group, since the other groups, with the exception of carbo-p-chlorobenzyloxy and carboallyloxy, as well as the peptide linkages themselves are not appreciably attacked for some time at low temperatures[4].

It can be said that catalytic hydrogenation works well with the groups, carbobenzyloxy, carbo-p-chlorobenzyloxy, carboallyloxy, carbophenyloxy, and carbo-p-tolyloxy. Since the peptide linkages are stable to catalytic hydrogenation and also to sodium in liquid ammonia, either of these reagents can be effectively used. The halogen acids have the

limitation that at high temperatures the peptide linkage as well as the blocking group are attacked, and therefore some blocking groups cannot be removed. Using this information, along with knowledge of the special reagents required for the tosyl, N-phthalyl, and formyl groups, it is theoretically possible to use five different blocking groups, each of which can be removed selectively, without an accompanying attack on the peptide linkages.

The first group which would be eliminated is the carbobenzyloxy group by the use of HBr in glacial acetic acid. Following this, the carbophenyloxy group can be effectively removed by catalytic hydrogenation. The tosyl group can be cleaved by the use of sodium in liquid ammonia. The fourth group to be removed would be the formyl group which can be selectively cleaved by HCl in alcohol. The last group to be removed would be the N-phthalyl group which could be removed by the use of hydrazine or phenylhydrazine.

Group / Reagent	carbo benzyl-oxy	carbo p-chloro benzyl oxy	carbo allyl oxy	carbo phenyl oxy	carbo tolyl oxy	tosyl	formyl	N-phthalyl
Catalytic Hydrogenation	good	good	mod.	good	good	none	none	none
Sodium in Liquid Ammonia	good	good	mod.	good	good	good	none	none
Phosphonium Iodide in Glacial Acetic Acid	good	good	mod.	none	none	none	none	none
HBr in Gla. Acetic Acid	good	good	good	mod.	none	none	none	none
HCl in Alcohol	poor	poor	poor	poor	poor	none	good	none

mod. moderately good

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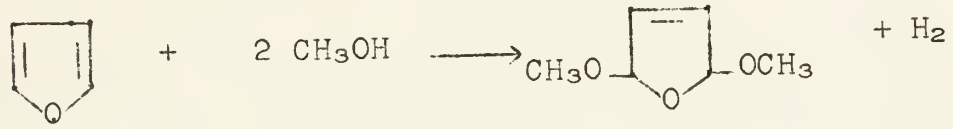
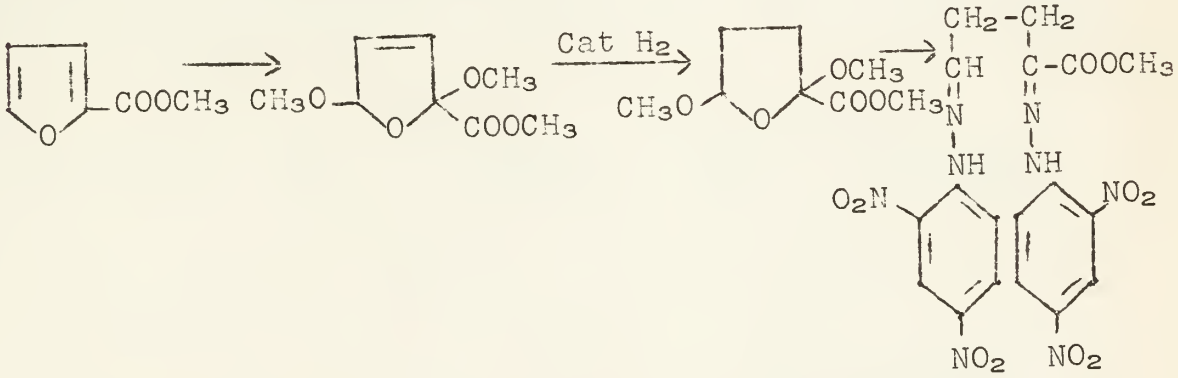
ELECTROLYTIC METHOXYLATION AND ETHOXYLATION OF FURANS

Reported by Debabrata Choudhury December 18, 195

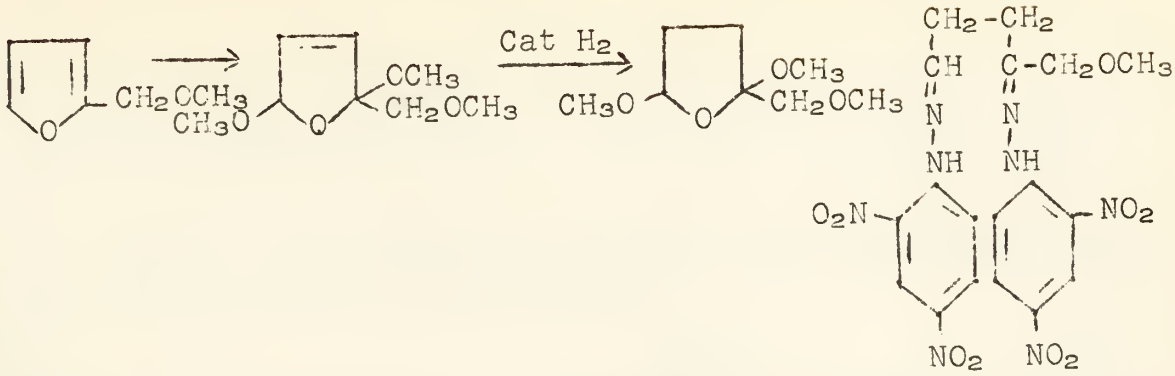
When furan is treated with a methanolic solution of bromine or chlorine it adds two methoxyl groups whereby 2,5-dimethoxy-2,5-dihydrofuran and two moles of hydrogen halide are formed. Dimethoxyfuran prepared in this way is often contaminated with a small amount of some halogen-containing impurity. A new method of methoxylation is developed by Clauson-Kaas and coworkers[1] which is simpler and gives a halogen-free reaction product. Furan is mixed with a methanolic solution of ammonium bromide and the mixture is electrolyzed. At the cathode, hydrogen and ammonia are formed and at the anode bromine is formed. The bromine reacts immediately with furan and methanol to give dimethoxydihydrofuran and hydrogen bromide. The hydrogen bromide and the ammonia from the cathode then regenerate the ammonium bromide. The net equation for the process is:



α-Substituted furans, silvan, furfuryl alcohol, furfuryl acetate and furfuryl dimethyl acetal can be methoxylated to the correspondingly substituted 2,5-dimethoxy,2,5-dihydrofuran in the same way[2]. If, instead of ammonium bromide, sulfuric acid is used, methoxylation can be made to proceed smoothly on negatively-(α)-substituted furans, and very high yields are recorded[3]. The methyl ester of dimethoxy dihydrofuroic acid, prepared in this manner, was hydrogenated catalytically to methyl dimethoxy tetrahydrofuroate. Using dinitro phenylhydrazine, the latter gave a bis-dinitro phenylhydrazone with the formula $C_{17}H_{13}O_9N_8(OCH_3)$, thus proving that the methoxy groups in both dimethoxy compounds are in the 2,5-positions.



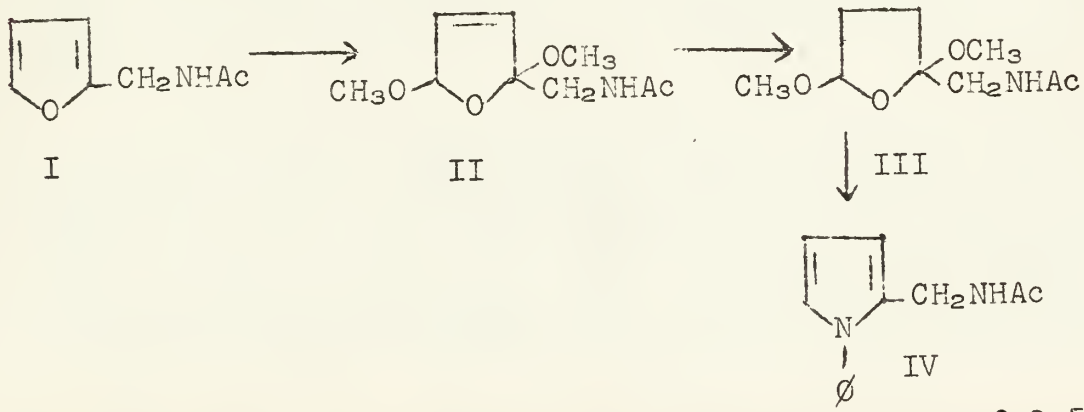
Furfuryl methyl ether can also be methoxylated by the electrolytic method,[4] and proof of the structure of the product was similarly effected:



The electrolytic method of methoxylation has been tried on β-substituted furans,[5] viz., β-isopropylfuran, 4-isopropyl-2-furaldehyde dimethyl acetal, and methyl 4-isopropylfuroate. All gave good yields of the corresponding dimethoxydihydrofurans. Furans can be ethoxylated using similar conditions replacing methanol by ethanol[6].

Yur'ev and his coworkers have described a method for transforming a furan into the corresponding pyrrole or N-substituted pyrrole. The furan and a large excess of an amine were passed, in the vapor phase, over aluminum oxide at about 400°, whereby pyrrole and water were formed. In this way Yur'ev prepared 14 pyrroles in moderate yields (3-41%). Thus, furan and aniline gave N-phenylpyrrole (24%).

Clauson-Kaas and coworkers[7] reported another route from furans to pyrroles. 2-(Acetamidomethyl)-furan (I) was methoxylated to 2,5-dimethoxy-2-(acetamidomethyl)-2,5-dihydrofuran (II), which was then hydrogenated catalytically to 2,5-dimethoxy-2-(acetamidomethyl)-tetrahydrofuran (III), which upon treatment with aniline in acetic acid gave N-phenyl-2-(acetamidomethyl)-pyrrole (IV). The overall yield of this three-step reaction was 81%.

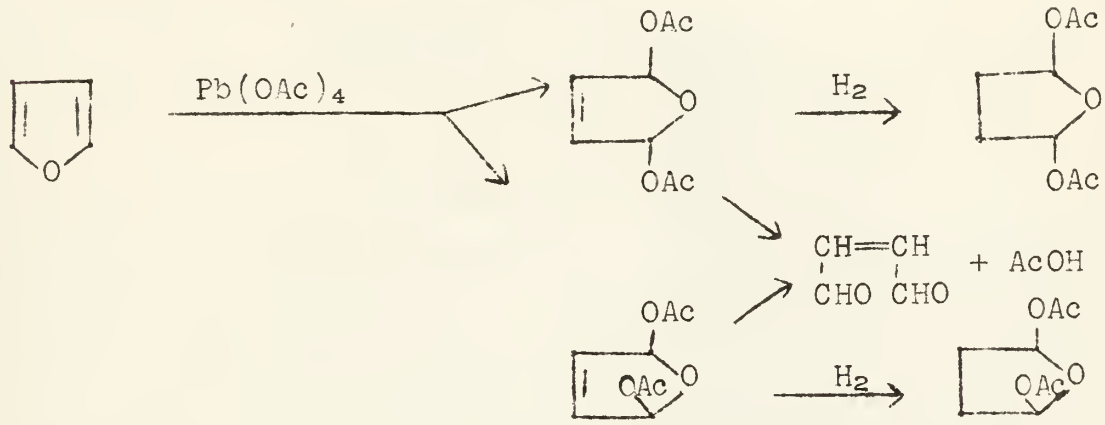


The transformation of furans into pyrroles by way of 2,5-dimethoxy tetrahydrofurans has now been used in the preparation of 15 different pyrroles. The results, together with

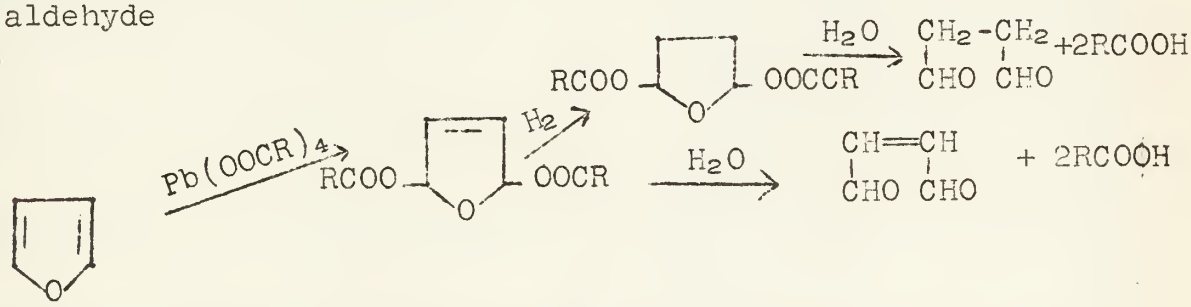
those by the method of Yur'ev, are summarized in table I.

It has been reported that electrolytic methoxylation of furans can be accomplished without using ammonium bromide. Instead, ammonium nitrate, sodium nitrate, sodium formate, boron trifluoride etherate, or sulfuric acid can be used[8].

Furan can be acetoxylated with lead tetraacetate[9]. The product is a mixture of two isomers, which can be separated by crystallization from methanol.



The isomers are hydrolysed to malealdehyde which proves that they both are 2,5-diacetoxy-2,5-dihydrofurans. The homologous 2,5-dipropionoxy- and 2,5-dibutyroxy-2,5-dihydrofurans can be prepared from furan and the corresponding lead salts. The structures of these new compounds were proved by the hydrolysis to malealdehyde and the corresponding aliphatic acids. Catalytic hydrogenation gave 2,5-dipropionoxy- and 2,5-dibutyroxytetrahydrofurans. Hydrolysis of these gave succinaldehyde



2,5-Dibenzoxy-2,5-dihydrofuran can also be prepared from furan and lead tetrabenzoate[9]. Hydrogenation gave a dibenzoxytetrahydrofuran which was hydrolyzed to succinaldehyde.

The pyrolysis of 2,5-diacetoxy-2,5-dihydrofuran gives a colorless liquid, $C_4H_3O_2(COCH_3)$, which has been shown to be 2-acetoxyfuran.[10] This acetoxyfuran has been used for the preparation of some 5-substituted 2-oxo-2,5-dihydrofurans[11]. With bromine it reacts to form 2-oxo-5-bromo-2,5-dihydrofuran. The reaction takes place rapidly at -5 to -10°C. In the same way 2-acetoxyfuran and chlorine give 2-oxo-5-chloro-2,5-dihydrofuran. With lead tetraacetate in acetic acid at

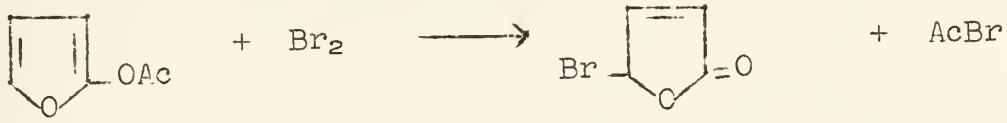
Table I. Pyrrole Compounds from Furans

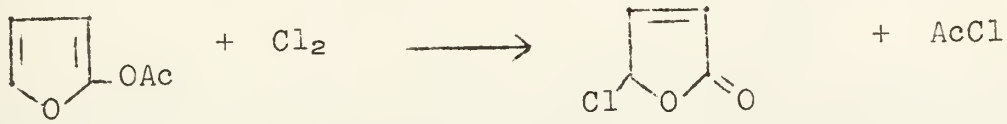
Furan Compound	RNH_2 Compound	Pyrrole Compound	Yields % based on the furan compound: Yur'ev's method (one step)	Yields % based on the furan compound: Electrolytic method (three steps)
Furan	Ammonia	Pyrrole	30	40
--	Methylamine	1-Methyl-pyrrole	25	-
--	Ethylamine	1-Ethyl-pyrrole	27	-
--	n-Butylamine	1-n-Butyl-pyrrole	-	21
--	n-Amylamine	1-n-Amyl-pyrrole	14	28
--	Aniline	1-Phenyl-pyrrole	24	59
--	o-Toluidine	1-o-Tolyl-pyrrole	41	54
--	p-Toluidine	1-p-Tolyl-pyrrole	21	-
--	Benzylamine	1-Benzyl-pyrrole	3	-
--	p-Phenylene-diamine	1,1'-p-phenylene dipyrryl	-	31
2-Methylfuran	Ammonia	2-Methyl-pyrrole	24	25
--	Aniline	1-Phenyl-2-methyl-pyrrole	12	51
--	o-Toluidine	1-o-Tolyl-2-methyl-pyrrole	10	-
--	p-Toluidine	1-p-Tolyl-2-methyl-pyrrole	10	-
2-(Acetamidomethyl)-furan	n-Amylamine	1-n-Amyl-2-(acetamidomethyl)-pyrrole	-	69
Furfuryl methyl ether	Aniline	1-Phenyl-2-(methoxy-methyl)-pyrrole	-	17
Furfural dimethyl acetal	Ammonia	2-Pyrrole-carboxaldehyde	-	24
--	Aniline	1-Phenyl-2-pyrrole-carboxaldehyde		35

(continued on next page)

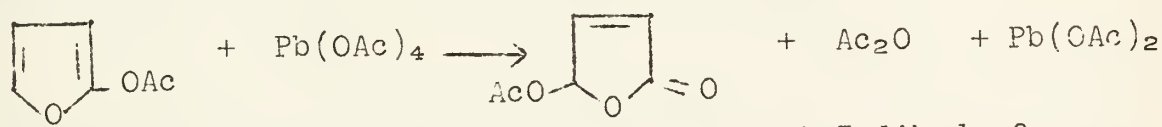
Table I (continued)

Methyl 2-furoate	Ammonia	Methyl 2-pyrrole-carboxylate	-	11
--	Aniline	Methyl 1-phenyl-2-pyrrole-carboxylate	-	36
2,5-Dimethylfuran	Ammonia	2,5-Dimethyl-pyrrole	16	-
2-Ethylfuran	Ammonia	2-Ethyl-pyrrole	5	-
3-Isopropylfuran	Aniline	1-Phenyl-3-isopropyl-pyrrole	-	35

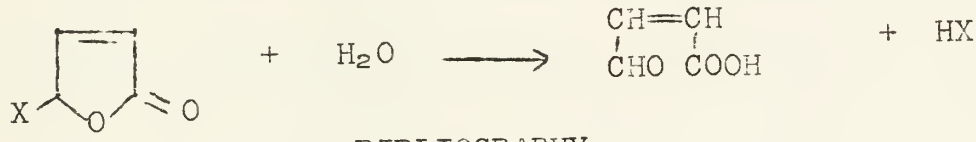




20-45°C. it gives 2-oxo-5-acetoxy-2,5-dihydrofuran. The



structure of the new 5-substituted-2-oxo-2,5-dihydrofurans was proved by hydrolysis to cis-β-formylacrylic acid, which was identified through its phenylhydrazone.



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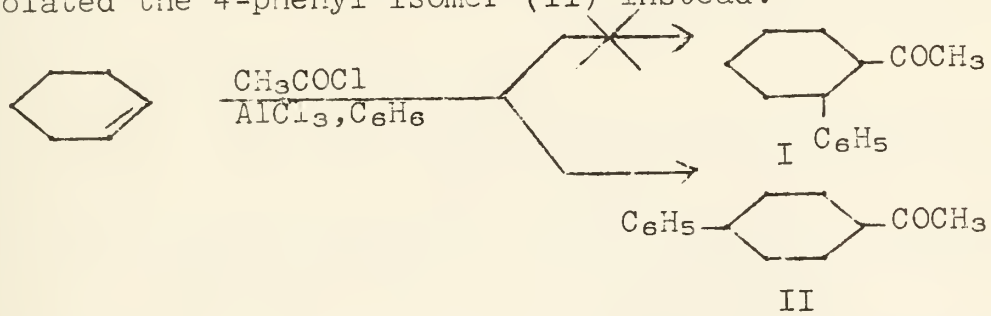
SOME MIGRATIONS ENCOUNTERED IN FRIEDEL-CRAFTS ACYLATIONS

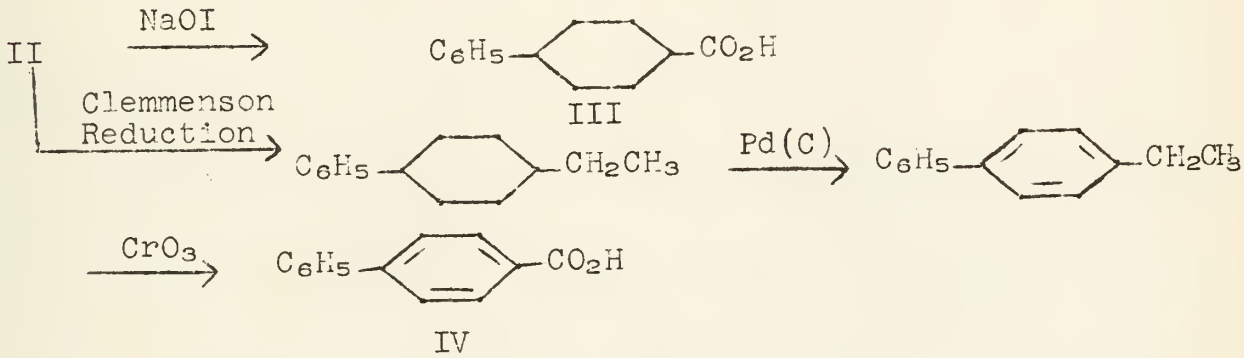
Reported by E. H. Hess January 8, 1954

Although the discovery of rearrangements of entering alkyl groups in Friedel-Crafts reactions is nearly as old as the reaction itself, it has been only in more recent years that abnormal products have been isolated from acylation reactions.

In 1935 Nenitzescu and Gavat[1] attempted to prepare 2-phenylcyclohexyl methyl ketone (I) for further synthetic work, but isolated the 4-phenyl isomer (II) instead.

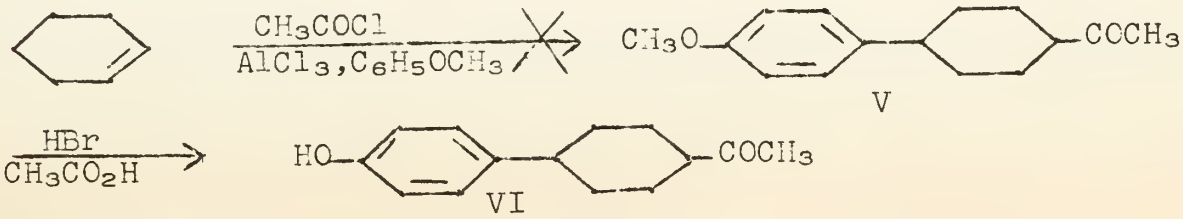


The structure of this isomeric compound was proved by hypohalite oxidation to the previously reported 4-phenylcyclohexanecarboxylic acid (III) and more vigorously proved by the three step conversion of II to p-phenylbenzoic acid (IV).



In further exploration of this reaction Nenitzescu found that an analogous migration occurred in the cyclopentyl series. Cyclopentene under the same reaction conditions yielded 3-phenylcyclopentyl methyl ketone. The structure of this compound was established by degradation to the carboxylic acid followed by an independent synthesis.

Somewhat later Johnson and Offenhauer[2] attempted to utilize this type of migration for synthetic purposes. They had hoped that anisole could be substituted for benzene in Nenitzescu's reaction so that the corresponding p-methoxy compound (V) would be formed. This attempt was unsuccessful. Nevertheless, they



did find it possible to synthesize compound VI by repeating Nenitzescu's work to get compound II which they then nitrated in the para position, reduced, diazotized and replaced by hydroxyl.

Migration in Open Chain Olefins

The next step in the study of the scope of this reaction concerned the behavior of open chain olefins in which there existed the possibility of migration of the entering phenyl group. In the series of olefins studied it was found that the phenyl group appeared on the methylene carbon farthest removed from the carbonyl group but was never found on the terminal position. These possibilities are illustrated below.

1. No migration possible

$$CH_2{=}CH_2 \xrightarrow[AlCl_3,C_6H_6]{CH_3COCl} C_6H_5\text{-}CH_2\text{-}CH_2COCH_3$$

2. Migration possible to methyl group but does not occur

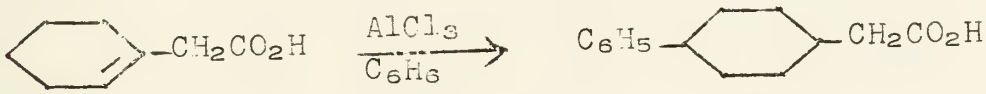
$$CH_3CH{=}CH_2 \xrightarrow{''} CH_3\text{-}\underset{\underset{C_6H_5}{|}}{CH}\text{-}CH_2COCH_3$$

3. Migration occurs to next methylene group

$$CH_3CH_2CH{=}CH_2 \xrightarrow{''} CH_3\text{-}\underset{\underset{C_6H_5}{|}}{CH}\text{-}CH_2CH_2COCH_3$$

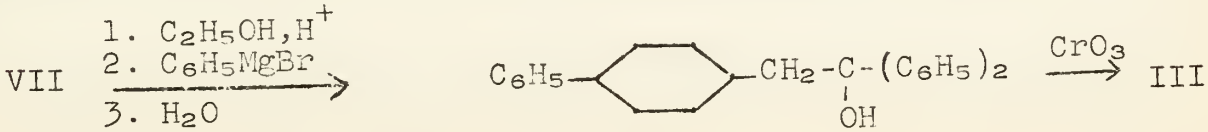
Migrations in α,β-Unsaturated Acids

Since the keto carbonyl group was observed to have the effect of pushing the entering substituent as far from it as possible, it was postulated that this same effect should be observed in the addition of benzene to α,β-unsaturated acids in the presence of aluminum chloride. This was tried with numerous cyclic and open chain acids and the same phenomenon was observed. Several interesting reactions described in a later paper by Nenitzescu and Gavat[3] showed that a carboxyl group attached to the side chain of a cyclohexane ring forced the entering phenyl group into the 4 position. The following transformation is illustrative:



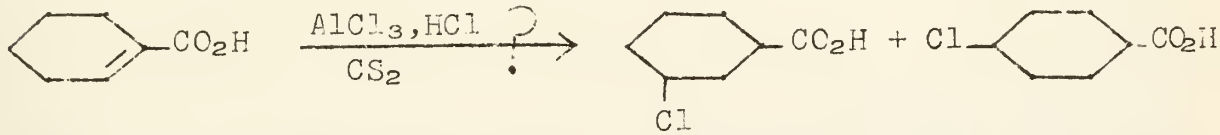
VII

The structure of VII was proved by relating it to its next lower homolog (III) which had already been identified.

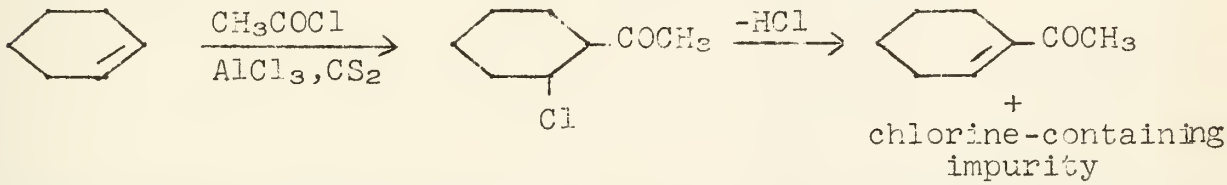


Isolation of the Rearranged Chloro Compounds

Even though these migrations had been originally postulated to proceed by a halogen migration step, no one until quite recently had isolated and definitely identified any of the rearranged chloro compounds. In later work on the reaction of cyclohexene-1-carboxylic acid with aluminum chloride and hydrogen chloride in an inert solvent Nenitzescu, Gavat and Cocora[4] did isolate a small amount of product which they supposed to be a mixture of 3-and 4-chlorocyclohexanecarboxylic acids.

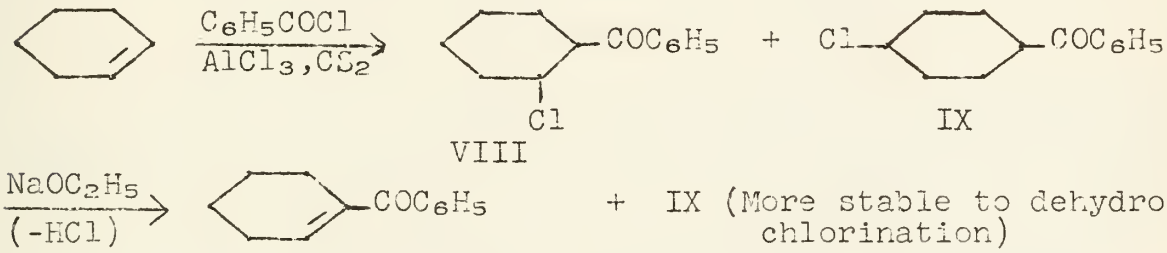


Royals and Hendry[5] had used the following reactions to prepare methyl 1-cyclohexenyl ketone and had reported a chlorine-containing impurity after the dehydrochlorination step.

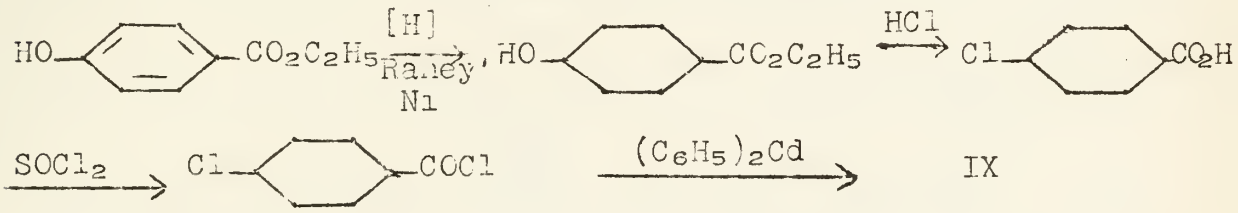


Fuson and Christ[6] had isolated a crystalline chlorine-containing byproduct from the analogous reaction using benzoyl chloride.

Stevens and Farkas[7] then studied the reaction of benzoyl chloride, cyclohexene and aluminum chloride in an attempt to isolate some of the rearrangement products. This was accomplished in the following manner, the 4-chloro isomer being obtained in 5-8% yields:



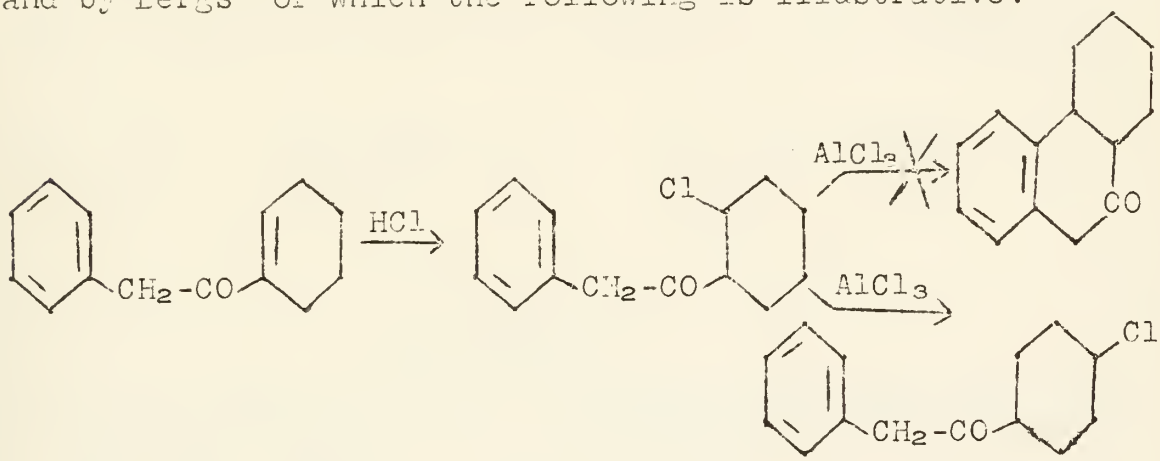
The structure proof of IX was accomplished by degradation studies followed by an independent synthesis.



It was also observed that rearrangement of the 2-chloro ketone (VIII) could be made to occur in the presence of aluminum chloride to give a small amount (8%) of the 4-chloro isomer (IX).

Mechanism of the Migrations

Nenitzescu and Gavat, in attempting to explain the migration phenomenon, assumed that a simple 1,2-addition of the acid chloride took place (in the case of the unsaturated acids, an addition of hydrogen chloride) followed by migration of the chlorine atom, which then reacted in a normal Friedel-Crafts manner. On this basis they explained the failure of several attempted ring closures reported earlier by Cook and Hewett[8] and by Bergs[9] of which the following is illustrative:



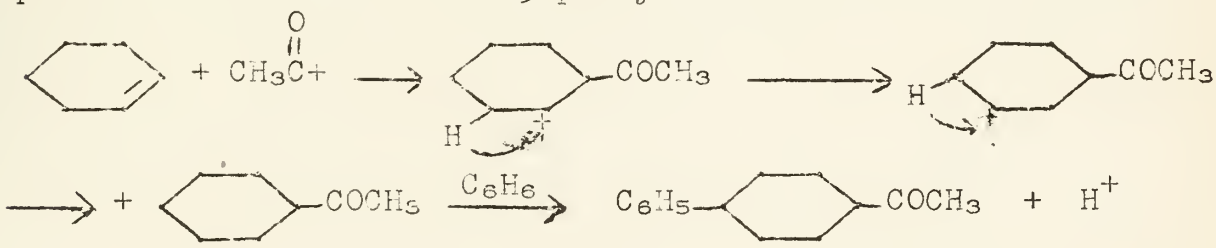
Nenitzescu's explanation of how the chlorine atom migrated was that a succession of hydrogen chloride eliminations and additions took place so that each time the chlorine moved from one carbon atom to the next. Johnson[10] in discussing this type of migration points out two other mechanisms by which this rearrangement could take place.

1. Direct migration of the phenyl group

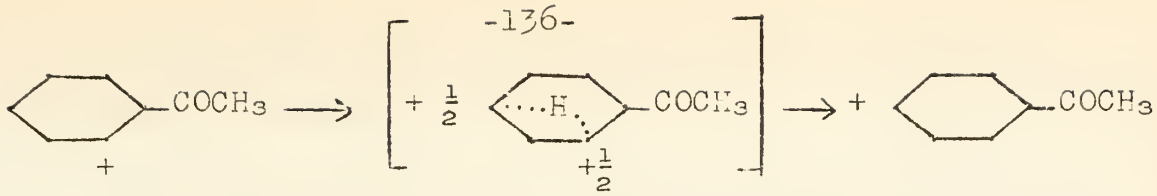
2. Three carbon tautomerism as shown below

$$-\overset{|}{C}H-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O \rightleftharpoons -\overset{|}{C}=\overset{|}{C}-\overset{|}{C}H-\overset{|}{C}=O$$

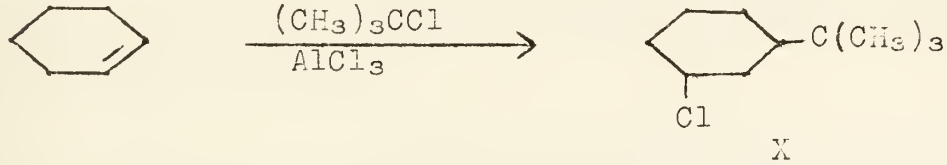
In the light of modern theory, however, this migration, whether to obtain the phenyl or the chloro compound, is more adequately explained by a carbonium ion rearrangement than by the shift of a chlorine atom or of a phenyl group. But the exact way in which this takes place, especially in the cyclic series, is not understood. If, in the case cited below, a double 1,2 hydride ion shift occurred, then it is indeed peculiar that none of the 3-phenyl isomer was ever isolated.



Another possibility would be that of a 1,3 hydride ion shift. This gains support since it is found that in many cases hydride ion shifts occur in a manner so that the transition state contains a 6-membered ring[11].



The other problem which remains unsolved involves the source of the driving force which causes the carbonium ion rearrangement. Stevens and Farkas[7] attributed the migration to the repulsion of the carbonium ion by the slightly positively charged carbonyl carbon. This theory breaks down, however, when it is noted that in the reaction of cyclohexene with t-butyl chloride some of the 3-chloro isomer (X) is formed[12].



X

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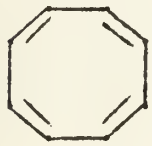
THE ELECTROLYTIC REDUCTION OF CYCLOOCTATETRAENE

Reported by Richard A. Strehlow January 8, 1954

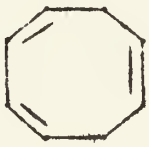
The synthesis of cyclooctatetraene (I) was first reported by Wilstatter[1,2]. After Reppe's synthesis of (I) from acetylene was reported[3], much interest was taken in the compound, its derivatives, and its reactions. The partial reduction of cyclooctatetraene has been the subject of several recent studies.[9]

The hydrogenation of (I) to cyclooctene has been described by Cope and Estes[4]. Sodium and methyl alcohol reduction of (I) has been reported to yield a mixture consisting of 1,4-cyclooctadiene, 1,5-cyclooctadiene, and possibly some 1,3-cyclooctadiene.[5]

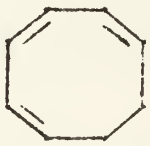
Since it was shown by Elofson[6] that (I) can be reduced polarographically, the electrolytic reduction of (I) was investigated by Craig, Elofson and Ressa[5]. The electrolysis was carried out at a mercury cathode in the presence of tetramethylammonium ions. 1,3,6-Cyclooctatriene (II) and 1,3,5-cyclooctatriene (III) were obtained in 84% yield. Of the mixed products, (II) was formed to the extent of about 75% and (III) to the extent of about 25%.



(I)



(II)



(III)

Tetramethylammonium ions were found to be necessary to give an efficient reduction. This was in agreement with the findings of Elofson[6], who had also determined that the reduction was not dependent on the hydrogen ion concentration and that the reduction involved the direct transfer of two electrons. These facts suggested that the primary electrode process was the formation of negatively charged ions of (I), which were stabilized in the presence of tetramethylammonium ions. Elofson did not formulate a structure involving the tetramethylammonium ion to explain the stability of the doubly charged anion of (I), but did suggest that (I) has a highly polarizable conjugated double bond system. This can be depicted by the following equation.

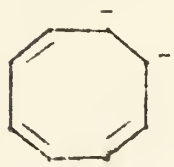
$$-HC{=}(CH{-}CH{=})_nCH- \xrightleftharpoons{(CH_3)_4N^+} -H\overset{+}{C}-(CH{=}CH-)_n\bar{C}H-$$

$$+2e^- \longrightarrow -H\bar{C}-(CH{=}CH-)_n\bar{C}H-$$

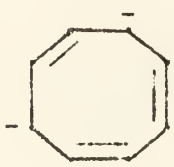
$$n = 0,\ 1,\ 2,\ \text{or}\ 3$$

For cyclooctatetraene, this is equivalent to drawing the two

structures (IV) and (V), of which (V) may be expected to be the better approximation. One might therefore expect the predominant product of the reaction to be 1,3,6-cyclo-octatriene.



IV



V

This is in agreement with the results of Craig, Elofson and Ressa who found a 3:1 predominance of (II) over (III).

A mixture of (II) and (III) was obtained in 61% yield by the treatment of (I) with sodium in liquid ammonia, according to Cope and Hochstein[7]. In this reaction (II) and (III) were obtained in approximately equal amounts. Similar results were obtained by treatment of (I) with lithium in ether followed by hydrolysis.

Craig, Elofson and Ressa reduced (I) with sodium in N-ethyl aniline and obtained a 74% yield of approximately equal amounts of (II) and (III). It was noticed that some isomerization took place, the 1,3,6-cyclooctatriene rearranging to 1,3,5-cyclooctatriene. The authors found the isomerization catalyzed by base. This fact seems to explain the relatively higher amounts of (III) obtained from sodium and lithium reductions of (I).

The same authors attempted the reduction of (I) with zinc and acetic acid and with lithium aluminum hydride. A small amount of triene formation was noticed in each case.

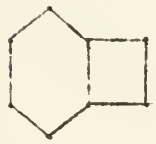
A summary of the results of various methods of reduction of (I) to (II) and (III) is made in Table 1.

Method used	% Yield	Relative amounts of (II)	(III) (approx)
Li in Et_2O	40-60	1	1
Na in NH_3(liq)	61	1	1
Na in N-ethyl-aniline (and Et_2O)	74	1	1
Electrolytic reduction	84	3	1
$LiAlH_4$	small	-	-
Zn in CH_3COOH	small	-	-

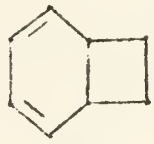
TABLE I

Cope and Hochstein found that the 1,3,5-cycloctatriene rearranges on heating to an isomer with a lower refractive index. They also found, after completely hydrogenating the mixture of products obtained from treating (I) with sodium and liquid ammonia, some bicyclo [4.2.0] octane (VI). They suggested that 1,3,5-cyclooctatriene may isomerize on heatin

to give a conjugated bicyco [4.2.0] octadiene such as (VII). This would be in harmony with the views of Friess and Boekelheide[8] who, by assuming the boat or tub form of cyclo-ŏctatetraene (VIII), sought to explain formation of bicyclic systems.



(VI)



(VII)

(VIII)

If the bicyclo compound is formed on heating 1,3,5-cycloŏctatriene, it should not be unexpected that Craig, Elofson and Ressa found no trace of bicyclic compounds in the electrolytic reduction product.

In summary, the electrolytic reduction of cycloŏcta-tetraene appears to afford the best route to 1,3,6-cyclo-ŏctatriene at the present time. The mechanism of the reaction has been examined in only a cursory manner and much work remains to be done.

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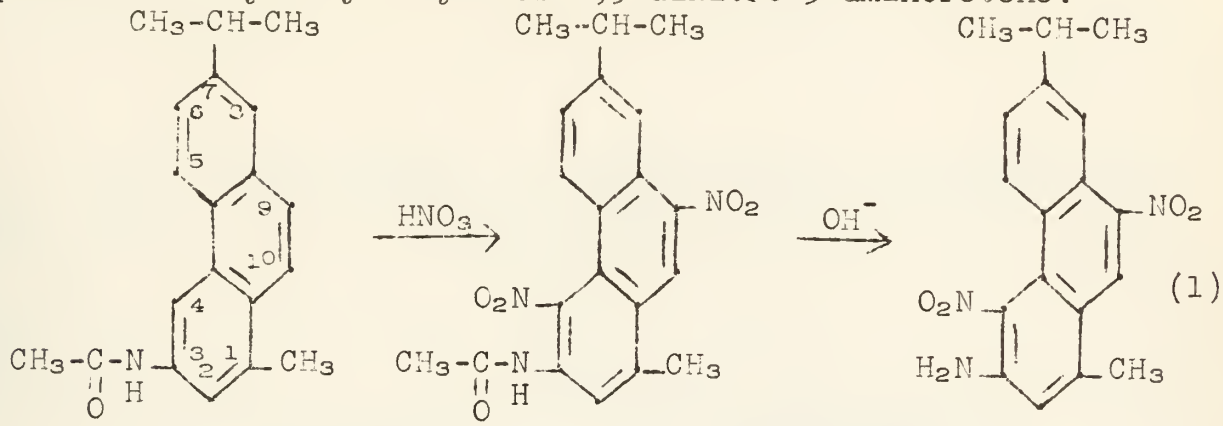
THE INTERACTION OF HALOGEN ACIDS AND NITRO AMINES

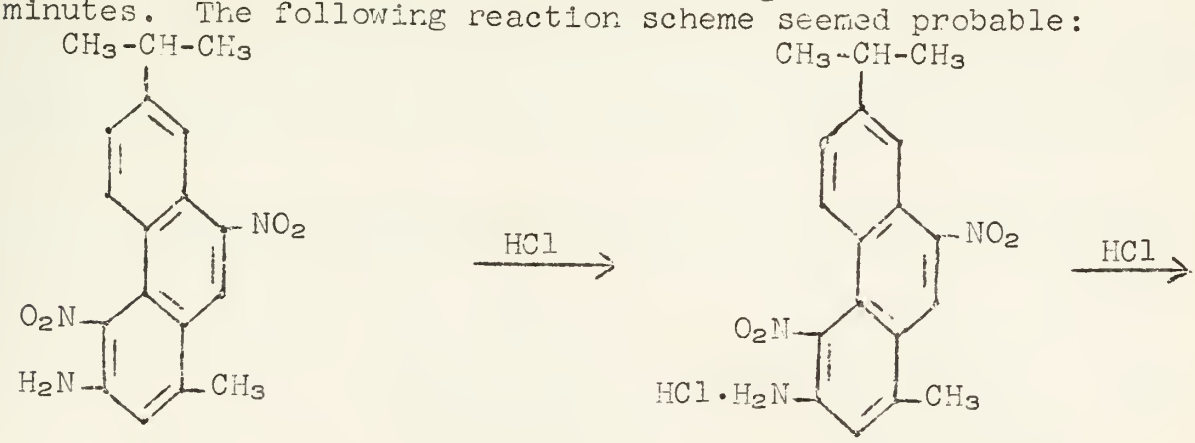
Reported by Edward P. Merica January 8, 1954

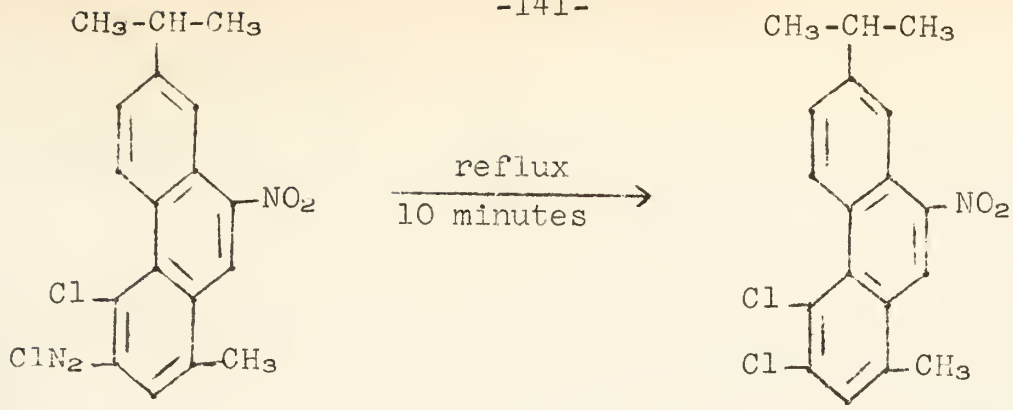
Nitration of 3-acetaminoretene results in a 3:2 ratio of 9-nitro-3-acetaminoretene and 4-nitro-3-acetaminoretene, and on nitration of both of these, 4,9-dinitro-3-acetaminoretene is produced[1]. Hydrolysis yields 4,9-dinitro-3-aminoretene.



The amine sulfate was readily prepared by dissolving 4,9-dinitro-3-aminoretene in concentrated sulfuric acid. However, when concentrated hydrochloric acid in glacial acetic acid was used in place of sulfuric acid the expected amine hydrochloride was not formed, and on refluxing, a gas was evolved and a solid product was obtained. The gas was shown to be nitrogen and analysis of the solid material revealed that two atoms of nitrogen had been eliminated and two chlorine atoms had entered the retene molecule.

The structure of this product was investigated by Sihlbom[2]. It did not have the properties of an amine but on reduction it yielded an amine, indicating that the nitro amine lost its amino group and one of its nitro groups on treatment with concentrated hydrochloric acid. When β-naphthol was added to the reaction mixture within one minute after the addition of hydrochloric acid, a red dye formed. It was assumed then that the first formed product was a diazonium salt. This diazonium salt was found to be stable for three days at room temperature but it was decomposed completely after being refluxed for 10 minutes. The following reaction scheme seemed probable:

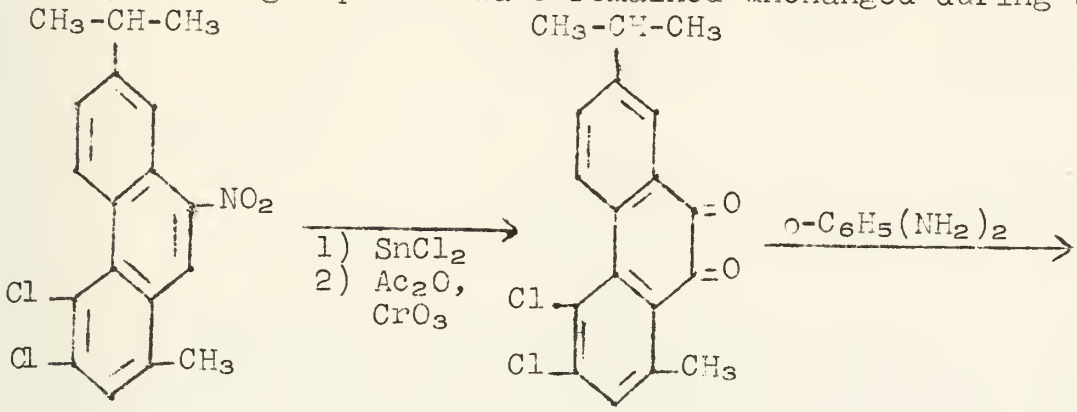


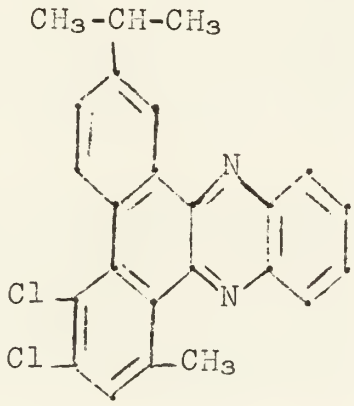


(2)

I

Since it was possible to convert I to a quinoxaline (II), the 9-nitro group must have remained unchanged during the di-





(3)

II

azotization and therefore the 4-nitro group was removed. It is reasonable to suppose that the chlorine atom entered the position vacated by the nitro group rather than another position. This has been shown to be the case in similar reactions by Dey, Maller and Pai[3].

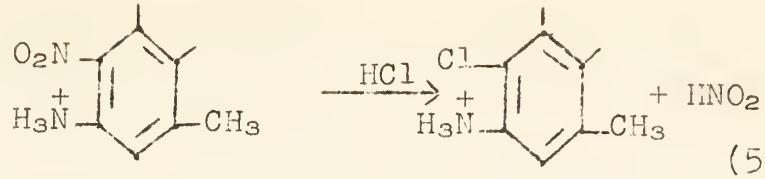
Two possible paths were proposed[4], one intramolecular (A) and one intermolecular (B):

A. Intramolecular

(4)

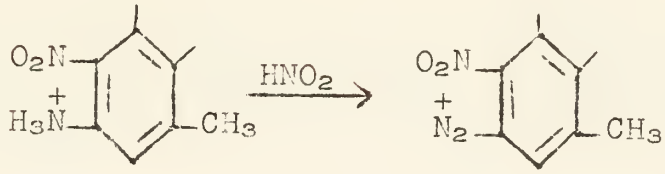
B. Intermolecular

Initiation:



(5)

Propagation:



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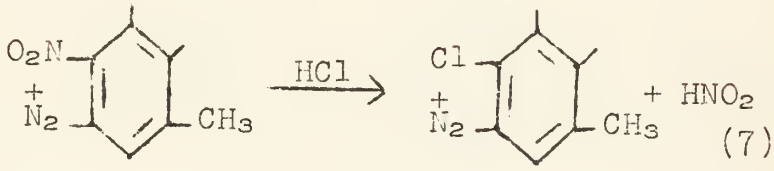
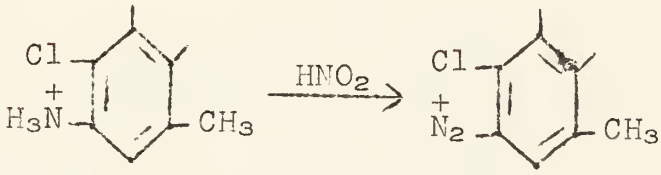


(7)

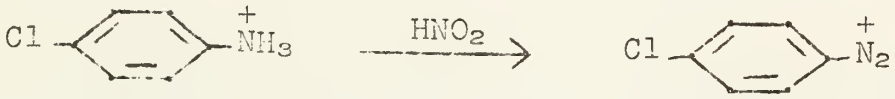
Termination:



(8)

The reaction of 4,9-dinitro-3-aminoretene with hydrochloric acid at 100° was complete in 20 seconds, but in the presence of an equimolar amount of p-chloroaniline, a reaction time of five minutes was required. After reduction of the diazonium salt with hypophosphorous acid, 4-chloro-9-nitro-3-aminoretene and 4-chloro-9-nitroretene were isolated in about 8% yield each, and after the Sandmeyer reaction p-dichlorobenzene (10%) and 3,4-dichloro-9-nitroretene (16%) were recovered.

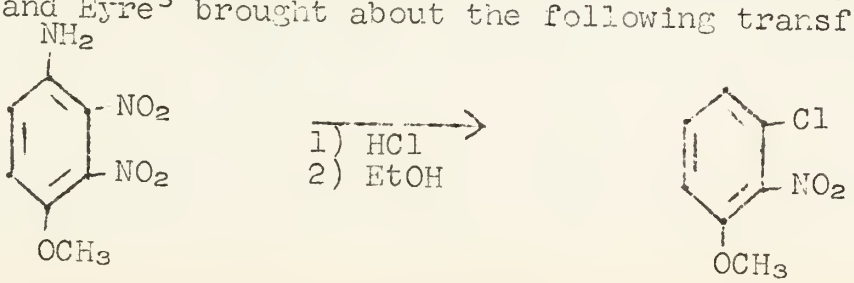
These results strongly support the intermolecular path (B). The diazotization of p-chloroaniline demonstrates that a diazotizing agent (represented in the scheme by HNO_2) is formed from dinitroaminoretene. The fact that the addition of p-chloroaniline decreases the rate of reaction points to a chain mechanism. By addition of an easily diazotized amine a new termination reaction (9) occurs and the total velocity is decreased.



(9)

On the other hand the velocity should be increased by the addition of a small amount of nitrous acid and this also was demonstrated.

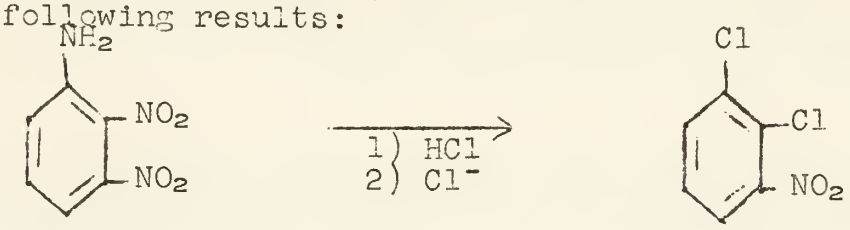
Reactions of this type were known as far back at 1902, when Meldola and Eyre[5] brought about the following transformation:



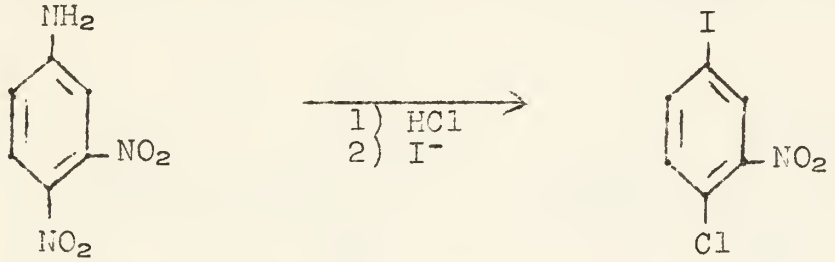
(10)

After an extensive study of other dinitroanisidines and polynitroanilines[6,7], Meldola formulated two rules governing such eliminations: a) the nitro group should be either ortho or para to the amino group, and b) there should be a second nitro group adjacent to the one displaced.

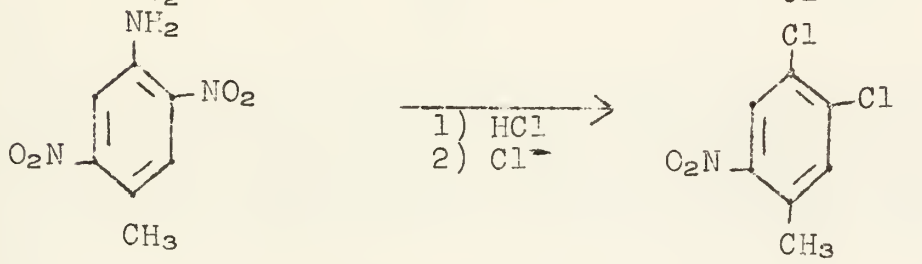
Meldola and his co-workers confined their investigations to heavily substituted nitroanilines, thereby leaving room for the possibility of steric influences operating to help such displacements take place. Dey, Maller and Pai[3] subjected 2,3- and 3,4-dinitroaniline and 2,5-dinitrotoluidine to this reaction with the following results:



(11)



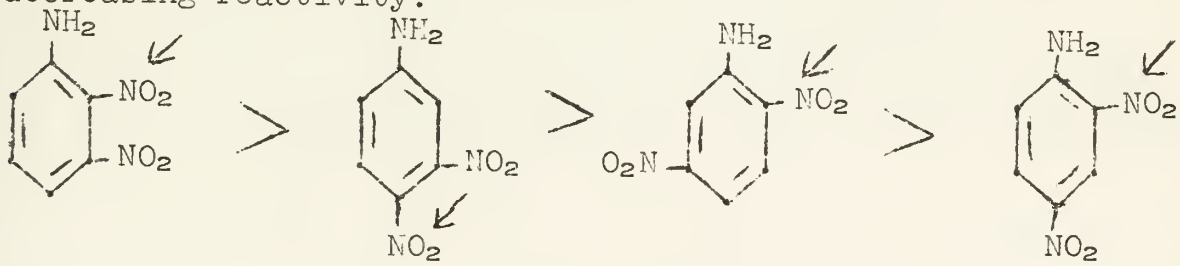
(12)



(13)

Reaction (12) could be explained only on the assumption that the 4-nitro group was replaced by chlorine in the course of the diazotization. Reaction (13) showed that Meldola's rules should be amended to read as follows: In a benzenoid dinitroamine where the nitro groups occur either ortho or para to each other, one of them is eliminated on treatment with hydrochloric acid, the eliminated group being either ortho or para to the diazo group.

Sihlbom[8] compared the relative reactivities of 2,3-, 2,4-, 3,4-, and 2,5-dinitroanilines and found the following order of decreasing reactivity:



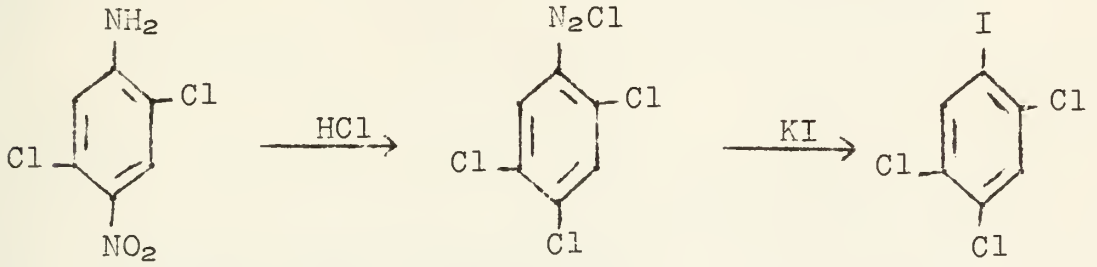
2,3- 3,4- 2,5- 2,4-

(Arrows point to nitro groups which were displaced)

This indicated that a nitro group in the o-position to the amino group is more reactive than one in the p-position, and that the reacting nitro group is activated more by an adjacent nitro group than by a p-nitro group. The latter in turn has a greater influence than a nitro group in the m-position.

Dey, Maller and Pai[3] have pointed out that the nucleophilic displacement of a nitro group is facilitated not only by the M and E effects of another nitro group in the ortho or para position, but also by the diazonium cation in the ortho or para position. Thus it has been observed that many nitro amines must be diazotized in non-aqueous solution; otherwise the nitro group is replaced by a hydroxyl group and a diazo-oxide is formed[9].

It has been found that the group ortho or para to the nitro group displaced need not be nitro[10]. For example, 2,4,5-trichloro-1-iodobenzene was obtained from 2,5-dichloro-4-nitroaniline:



(14)

Sihlbom found that hydrochloric acid could be replaced by hydrobromic acid in the reaction with dinitroaminoretene[2] but not with the dinitroanilines[8]. Other carboxylic acids such as formic and lactic could be used instead of acetic acid. Ethanol and acetone were unsatisfactory solvents but water gave fair results.

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SEMINAR TOPICS

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AROMATIC RING COMPLEXES

Reported by George P. Scott February 12, 1954

Introduction - - - Evidence that aromatic hydrocarbons and their derivatives can form loose addition compounds or "complexes" has been accumulating in the literature since 1877[1] and is still the object of intensive study. An understanding of the part they play in the reactions of aromatic molecules is considered essential to nearly all theoretical treatments.

In some cases these complexes can actually be isolated; more often their existence has been inferred from such evidence as solubilities, vapor pressures, color of solution, ultra-violet absorption bands, and from equilibrium or kinetic data. The most important types reported in the literature are listed in Table I with appropriate references.

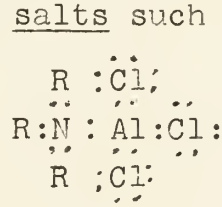
Table I

TYPES OF AROMATIC RING COMPLEX REPORTED IN THE LITERATURE

Complexing Agent	Key References
Metal Halides ($AlCl_3$ etc.)	1,2,3,4,5
Picric Acid (and other polynitro cpds.)	6
Protons (H^+)	7
Sulfur Dioxide (SO_2)	8
Silver Ion (Ag^+)	9
Halogens (Cl_2, Br_2, I_2)	10,11,12
Oxygen (O_2)	13
Reaction Intermediates	7,14,15

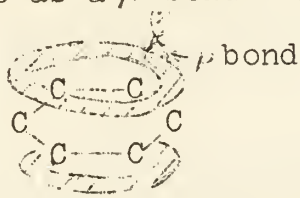
Although the stability of these complexes varies considerably, most of them are relatively unstable. Values of the order of 2 to 3 kcal. have recently been reported for the heats of formation of certain aluminum bromide complexes[2].

The Basicity of Aromatic Hydrocarbons - - - Inspection of Table I shows that most of the complexing agents are acidic in nature, and most investigators agree that the complexes are analogous to Lewis salts such as:



and that the hydrocarbons are behaving as weak bases. This view is supported by the fact that, with a few exceptions to be discussed later, there is very good correlation between increased stability of the complexes and greater electron donating tendencies of ring substituents[2,7,11]. However, aromatic hydrocarbons have no unique pair of electrons to donate such as the unshaired pair of p electrons in amines.

The π Complex Theory - - - According to the molecular orbital concept of valence, aromatic rings posses systems of π orbitals arranged in two doughnut-shaped lobes (of opposite sign in ψ) above and below the plane of the ring, containing (usually 6) loosely bound electrons. M. J. S. Dewar[14,15] has proposed that aromatic ring complexes are bound together by virtue of the overlap of the electron-rich π system in the ring with some electron-poor or vacant orbital in the complexing agent to form what he refers to as a μ bond. Dewar has expanded this



idea into a rather comprehensive theory of aromatic and ethylenic reaction mechanisms known as the "π complex theory". In this theory π complexes are proposed as key intermediates in a wide variety of aromatic and aliphatic reactions. The most important arguments advanced in support of this theory are as follows:

1. It explains the basic properties of aromatic rings.
2. The π complexes can form without loss of much ring resonance and are therefore <u>lower energy</u> intermediates than classical structures.
3. It offers an obvious explanation of why only electrophilic (cationic) reagents normally react with double bonds and aromatic rings.
4. It offers an explanation of the puzzling ring migrations and para rearrangements[16] by providing an "electronic tramway" to serve as a migration path.

At the present time most authors accept π complex structures for many of the complexes listed in table I[2,7,12,17], but many of the reaction mechanism interpretations involving π complex intermediates have been strongly criticized[15,18,19].

The Benzidine Rearrangement Problem - - - There is strong evidence[20] that the rearrangements of hydrazobenzenes to benzidines and other products occur without separation of the two rings. Dewars explanation of this reaction is one of the most unique applications of the π complex theory. It involves the following steps:

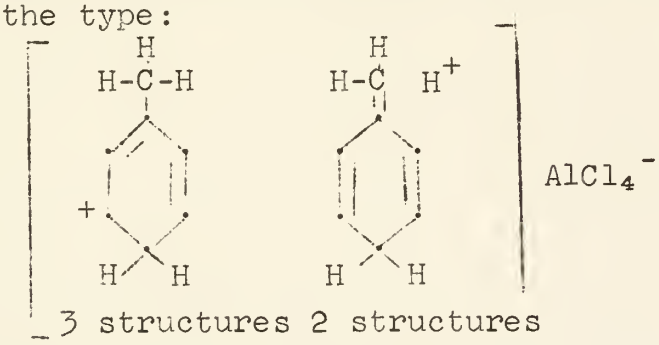
1. Neutralization of <u>one</u> basic nitrogen to form $C_6H_5N^{+}\text{-}NC_6H_5$
   H_2H
2. Folding of the two rings (A)
3. Expansion of the N-N bond to form a μ bond. (The ring with the + charge is electron-poor; the other is electron rich.) (B).
4. Unfolding to give the benzidine configuration (C).

A B C

The formation of by-products (diphenylenes and semidines) was explained by postulating that the complex rotated at stage B.

This mechanism has been attacked by Hammond[19], who showed the rate was second order with respect to H_3O^+ ion concentration, which is inconsistent with the assumption that the rate-controlling step involves the first cojugate base of hydrazobenzene only. In reply to this[15] Dewar suggested that the second proton was essential to the unfolding step (4). The recent finding of Carlin[21] that the rearrangement of o-hydrazotoluene has an order of 1.6 with respect to H_3O^+ ion concentration emphasizes the need for further work before the benzidine problem can be resolved.

<u>π and σ Complexes</u> - - - The work of Brown[2,3,4,7] suggests that <u>two</u> types of complex, π and σ (classical), can exist and may be involved in reaction mechanisms. Henry's Law constants of HCl dissolved in dilute heptane solutions of various hydrocarbons, in general, parallel the basicities to be expected from electron shifts[7]. In comparisons of certain alkylated hydrocarbons using the HCl technique, the basicity order is just the reverse of the order based upon the stabilities of $AR \cdot BF_3 \cdot HF$ complexes[5]. It is also the reverse of halogenation rates. It is therefore proposed that the "Friedel - Crafts" complexes, which contain both metal halide and hydrogen halide, have a "classical" structure of the type:



in which hyperconjugation can occur. This type of complex is more stable and requires longer to form. The solutions are colored, conduct current, and will allow deuterium exchange to the ring. He suggests that most ring-substitution intermediates are of this type.

On the other hand the $AR \cdot HCl$ complexes and many other less stable types are π complexes. Recently Brown has presented evidence that unstable complexes of the formula $AR \cdot Al_2Cl_6$ can also exist[2]. These he believes to be π complexes.

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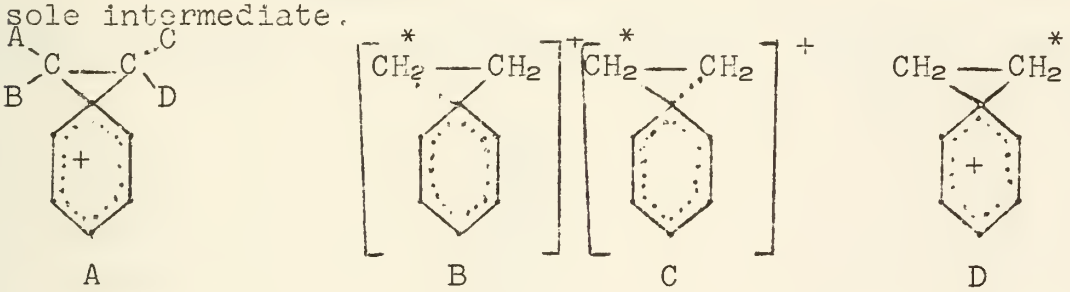
MOLECULAR REARRANGEMENTS

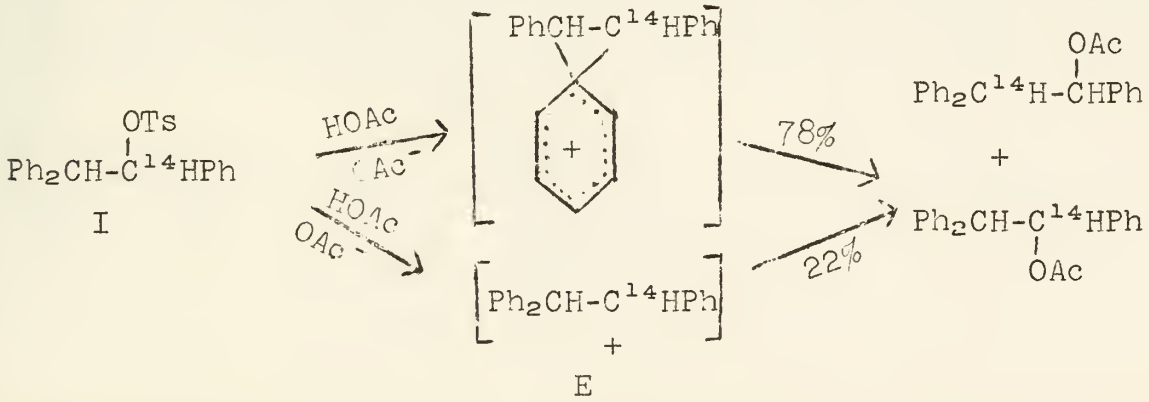
Reported by J. F. Mills February 12, 1954

Cram in 1949 introduced[1,2] the concept of the symmetrical phenonium ion (A) as a discrete reaction intermediate of geometrical stability to explain the stereochemical results he observed on acetolyzing the p-toluenesulfonate esters of the diastereomeric 3-phenyl-2-butanols. This interpretation was later expanded[3] to the view that bridge cations such as A existed in solution with tosylate anions as ion pairs. Later the stereochemical consequences of the solvolysis of various 4-phenyl-3-hexanol derivatives[4] and the radiochemical consequences of nitrous acid deamination of 2-phenylethylamine-1-C^{14} were studied[5] and the results of neither investigation could be explained in terms of symmetrical phenonium ion alone.

Roberts has proposed[5] structures similar to B and C for the cationic intermediate formed during nitrous acid conversion of 2-phenylethylamine-1-C^{14} to 2-phenylethanol-1,2-C^{14}, and suggested that cation B underwent reaction with hydroxyl ion more rapidly than it equilibrated with C. This hypothesis rationalized Roberts's observation that neither phenyl nor substituted phenyl migration ever approached 50% as should be the case if the symmetrical phenonium ion D were in fact the sole intermediate.

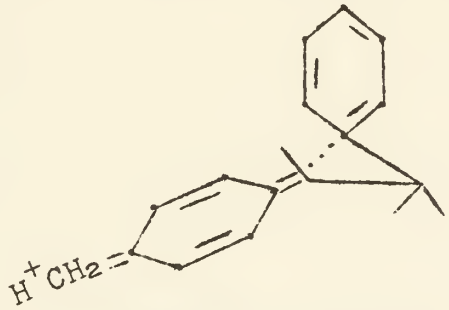


Although the stereochemical studies of Cram[1,3] have precluded the contribution of ions like E, the radiochemical data of Bonner and Collins[6] indicate that during acetolysis of tosylate (I), the ion E must be involved to the extent of approximately 22%. That this 22% acetolysis which proceeds without phenyl migration does not occur through a second-order displacement of tosylate by acetate ion is suggested by the fact that increasing the acetate ion concentration several fold does not appreciably diminish the extent of phenyl migration.



Bonner and Collins also reported[6] that the formolysis of the tosylate I proceeded with elimination, yielding the corresponding olefin in which a net 50% phenyl migration had taken place. However, the possibility of a formate intermediate rearranging via a carbonium ion mechanism has not been excluded in this work.

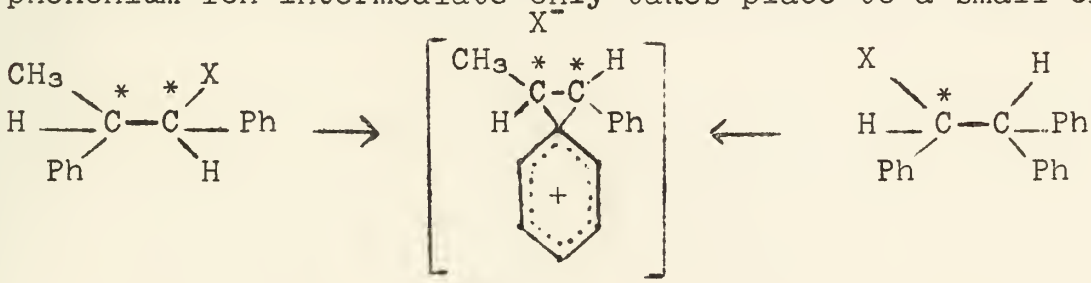
Burr has made a study[7] of the relative acetolysis rates and migration ratios in the phenyl and tolyl substituted ethyl tosylate series. As was expected[8] the substitution of p-tolyl groups for phenyl groups increased the rate of the rearrangement reaction. It was also observed that a methyl group in the non-migrating aryl would enhance the rate for a migrating tolyl and phenyl group. From these results it appears that a structure such as II might well be a contributing factor in pushing off the migrating group in a phenonium ion intermediate.



II

Migrating Group	Non-migrating Group	[9]Relative Acetolysis Rate per Aryl
C_6H_5	C_6H_5	1.0
C_7H_7	C_6H_5	4.90
C_6H_5	C_7H_7	1.93
C_7H_7	C_7H_7	4.50

Recently Cram has observed[10] the solvolysis of optically pure 1,1-diphenyl-2-propyl p-bromobenzenesulfonate in acetic acid gave a mixture of partially racemic acetate, and of optically pure threo and erythro acetates. The ratio of threo to erythro isomers was the same as that obtained from a solvolysis of threo 1,2-diphenyl-1-propyl p-bromobenzenesulfonate under the same conditions, a fact which suggests a common intermediate (a transphenonium ion) for the two processes. However, the ratio of the amounts of racemic acetate to the threo and erythro acetates indicates that the process via the phenonium ion intermediate only takes place to a small extent.



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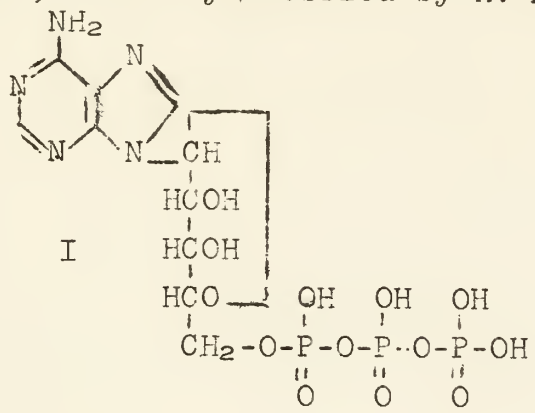
ATP: its Synthesis and Some of its Properties

Reported by E. Richter February 26, 1954

The mononucleotide adenosine triphosphate (I) or ATP, as it is now generally abbreviated, is a monoalkyl ester of a polyphosphoric acid. It is the triphosphoric acid ester of the nucleoside adenosine[1,2] and as such is composed of three different classes of compounds: a heterocyclic base, adenine or 6-aminopurine; a carbohydrate, D-ribose; and three molecules of phosphoric acid. The "linear chain" of the three condensed molecules of phosphoric acid is attached to the 5'-position of the adenosine[1,2]. Adenosine is the common name of 9-β-D-ribofuranosido-adenine[3], first synthesized by A. R. Todd (1948)[4].



I

ATP derives its interest from the important role it plays in the physiology of living matter. A few of the more important examples will clearly illustrate this:

1) Dephosphorylation of ATP is the primary process during the contractile phase of muscle contraction[5],

2) Activation of acetate as acetyl-coenzyme A is a reaction which involves ATP[6,7,8],

3) Krebs or citric acid cycle oxidation requires ATP[9],

4) Hexose + ATP $\xrightarrow{\text{hexokinase}}$ glucose-6-phosphate + adenosine diphosphate[10],

5) Fructose-6-phosphate + ATP $\xrightarrow{\text{phosphofructokinase}}$ fructose-1,6-diphosphate + adenosine diphosphate[11],

6) Glucose-1-phosphate + ATP $\xrightarrow{\text{glucose diphosphate kinase}}$ glucose-1,6-diphosphate + adenosine diphosphate[12],

7) 2 adenosine diphosphate $\xrightarrow{\text{adenylic kinase}}$ ATP + adenosine monophosphate[13,14]

8) 1,3-Diphosphoglyceric acid + adenosine diphosphate $\xrightarrow{\text{phosphoglyceric kinase}}$ 3-phosphoglyceric acid + ATP[15],

9) Diphosphopyridine nucleotide (coenzyme 1) + ATP $\xrightarrow{\text{triphosphopyridine nucleotide synthetase}}$ triphosphopyridine nucleotide (coenzyme 2) + adenosine diphosphate[16].

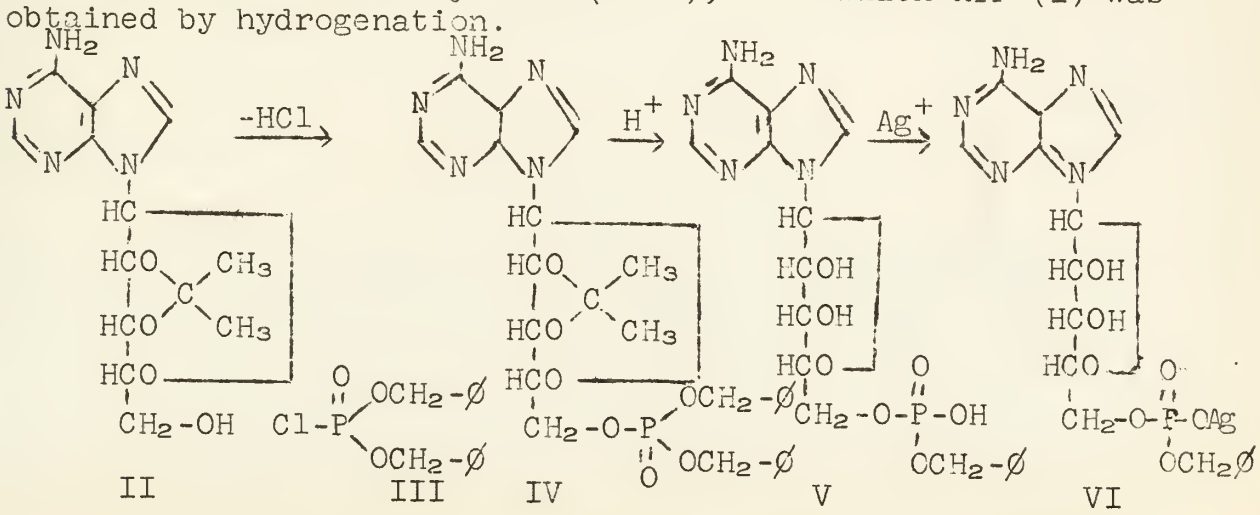
ATP was discovered in muscle tissue by Lohmann[17] and by Fiske and Subrarow[18] in 1929. It was later found in human blood and in yeast[19-21] and mung beans[22]. It can be prepared from an

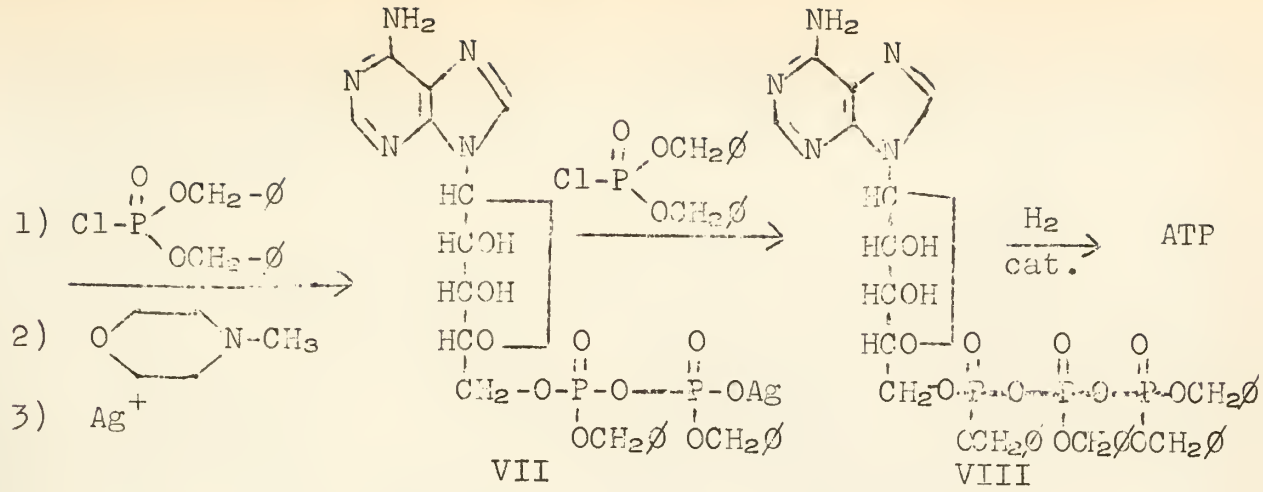
extract of frog or rabbit muscle by precipitation as the barium calcium or mercury salt after the protein has been removed with trichloroacetic acid[23-27]. The white, solid ATP and its sodium salt are readily soluble in water, while the salts that it forms with several heavy metals[28] are insoluble; the two different acridinium salts[28,29] can be recrystallized from water. Formation of crystalline alkaloid salts has also been reported[30]. On acid hydrolysis ATP gives adenine, D-ribose-5'-phosphate and two moles of phosphoric acid[17]. It reacts with only one mole of periodate[2], which shows that the 2' and 3'α-glycol hydroxyls are unsubstituted. Nitrous acid converts the amino group into a hydroxyl group[31].

ATP has been prepared by enzymatic phosphorylation of adenosine-5'-phosphate with hexose diphosphate and phosphopyruvic acid (1935)[21]. It has also been synthesized by enzymatic phosphorylation of adenosine with inorganic phosphate[32] and fructose diphosphate as well as phosphoglyceric acid (1937)[33].

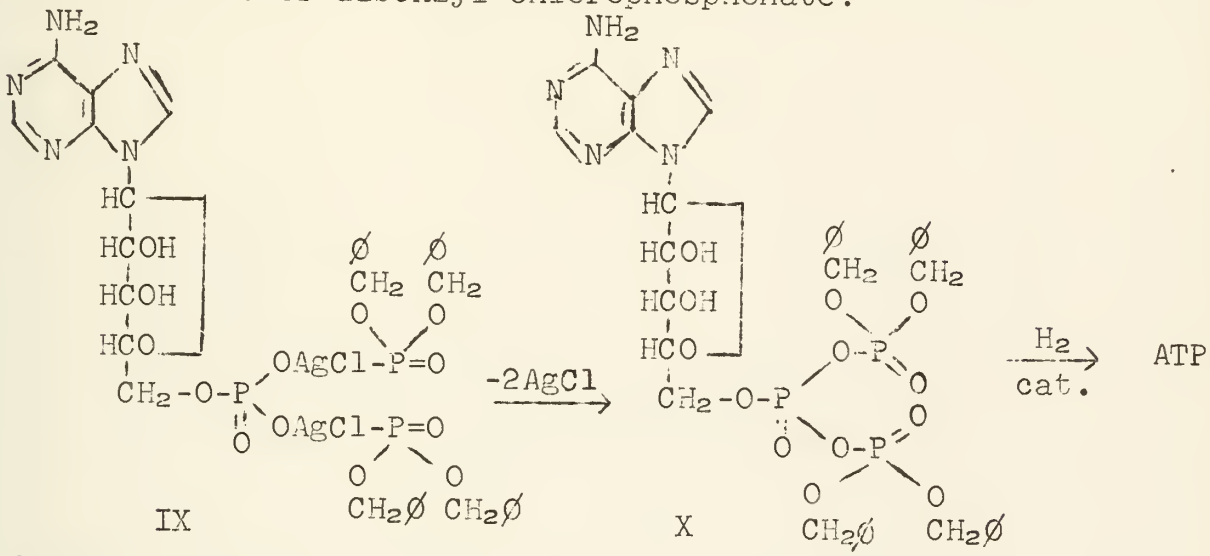
The chemical synthesis of ATP was performed by A. R. Todd's group at Cambridge. Adenosine, which is available through enzymatic or chemical degradation of yeast nucleic acid[34], was the basic raw material. Through the protection of its 2' and 3' hydroxyls by acetyls or the isopropylidene group it was transformed into the suitable starting materials 2',3'-diacetyladenosine and 2',3'-isopropylideneadenosine. Both were already known from Levene's pioneer work in nucleotide chemistry[35].

In the first synthesis (1949)[29] dibenzyl chlorophosphonate (III) was used throughout as the phosphorylating reagent. Its application to 2',3'-isopropylidene adenosine (II) led to 2',3'-isopropylidene adenosine-5'-dibenzylphosphate (VI). (This, at the same time, offered an improved synthesis of adenosine monophosphate, AMP[36], over Bredereck's preparation which employed diphenyl chlorophosphonate[37].) Mild acid treatment of the dibenzyl phosphate (IV) removed the isopropylidene group and one benzyl group, giving adenosine-5'-monobenzyl phosphate (V) which is an ideal substance for further phosphorylation. Its silver salt (VI) reacted with dibenzyl chlorophosphonate with elimination of silver chloride to yield adenosine-5'-tribenzyl diphosphate. This compound was partially debenzylated with N-methylmorpholine (complete debenzylation gave adenosine diphosphate, ADP[36]) and again a silver salt (VII) was prepared. With another molecule of dibenzyl chlorophosphonate this silver salt produced tetrabenzyl-ATP (VIII), from which ATP (I) was obtained by hydrogenation.

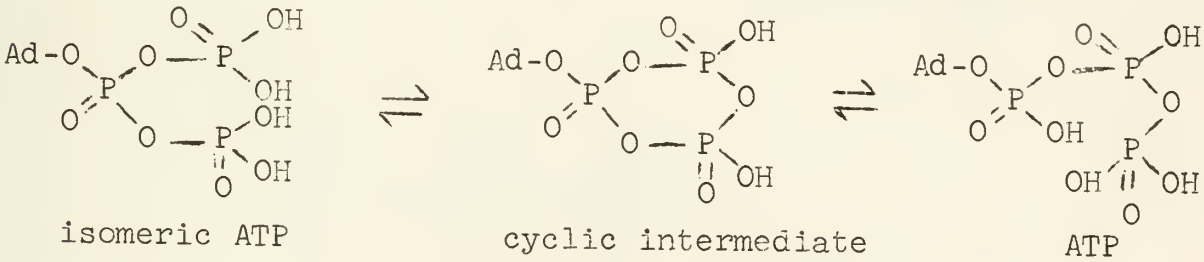




In a second and simpler synthesis (1949)[38] the disilver salt of adenosine-5'-phosphate (IX) was allowed to react with two molecules of dibenzyl chlorophosphonate:



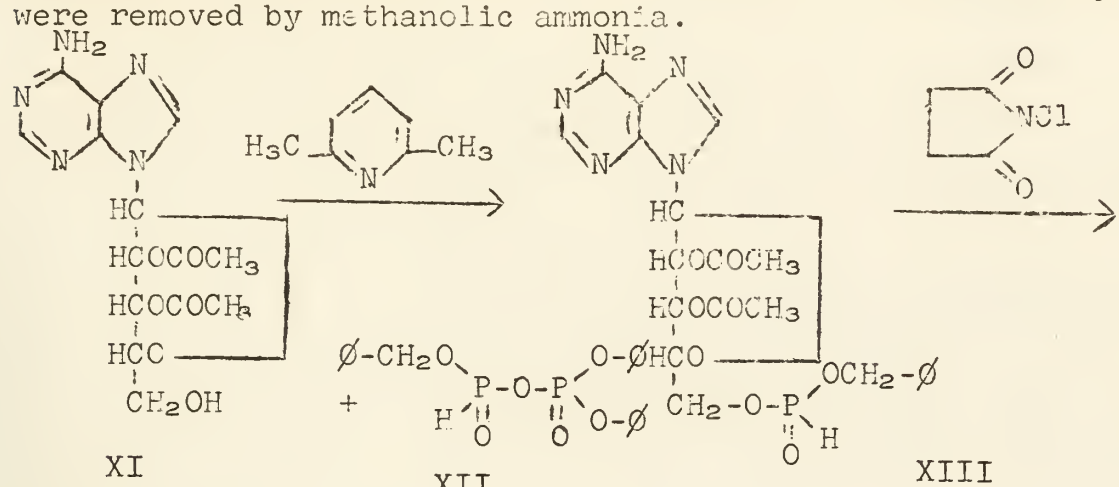
The product which was obtained after hydrogenation of X was identical with natural ATP and the one prepared by the previous synthesis. To explain this unexpected result, Todd and Michelson[38] assume that the two isomers are in equilibrium through a cyclic intermediate:

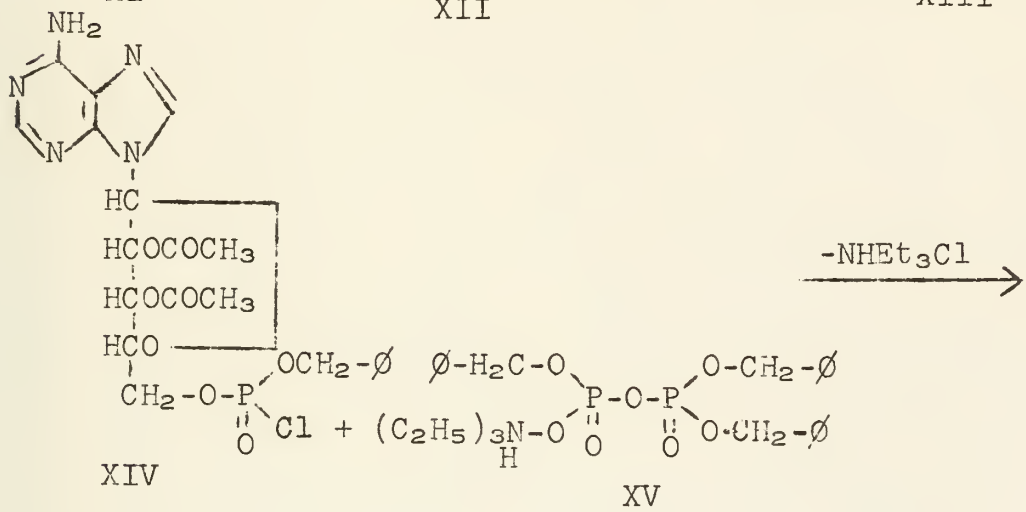


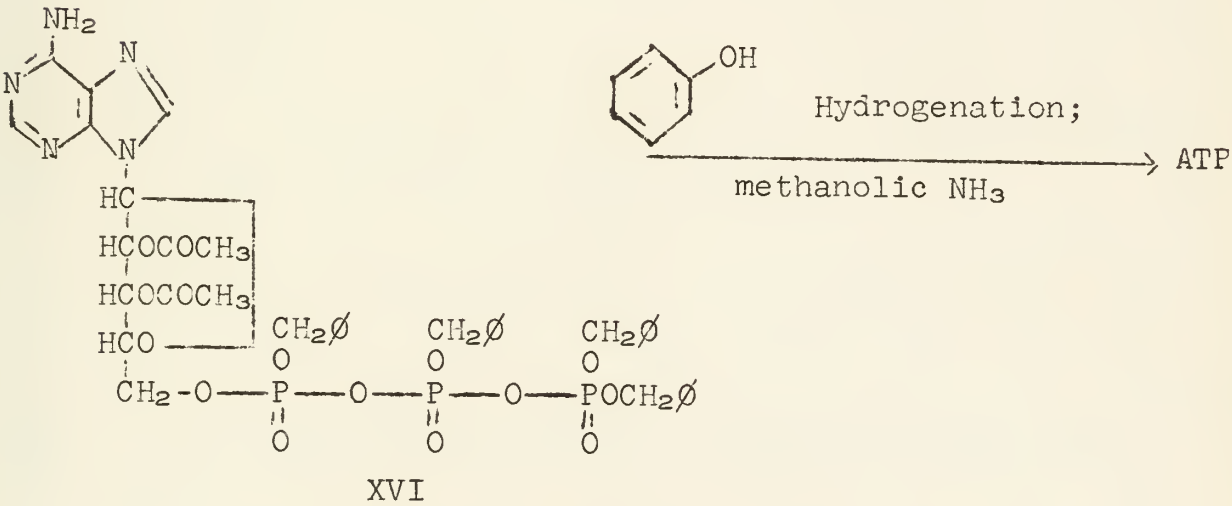
Ad = adenosine residue

In a third synthesis (1953)[39] 2',3'-diacetyl adenosine (XI) was phosphitylated with O,O-diphenylphosphoric O-benzylphosphorous anhydride (XII)[40], a "mixed anhydride", to give 2',3'-diacetyl adenosine-5'-benzylphosphite (XIII). This was chlorinated with N-chlorosuccinimide, and the resulting 2',3'-diacetyl adenosine-5'-benzylchlorophosphonate (XIV) was condensed with triethylammonium tribenzyl pyrophosphate (XV)[41]. The 2',3'-diacetyl adenosine-5'-tetrabenzyl triphosphate (2',3'-diacetyl tetrabenzyl-ATP) (XVI), which was obtained in good

yield, showed some resistence towards debenzylation. It could, however, be freed of its benzyl groups by treatment with phenol or cresol followed by hydrogenation. The 2' and 3' acetyls were removed by methanolic ammonia.







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CATIONIC CATALYZED COPOLYMERIZATION

Reported by David Tanner February 26, 1954

There are three different ways to initiate a polymerization and convert an olefin to a high polymer. These are the addition of: (1) a free radical, (2) a carbonium ion, or (3) a carbanion to the double bond. Catalysts for these three elementary reactions are peroxides, Lewis acids ($AlBr_3$, $SnCl_4$) or organometallic compounds respectively.

When two different polymerizeable olefins or monomers are mixed together in the presence of an ionic or a free radical initiator both of these monomers may be incorporated in the polymer chain. The composition of this copolymer is largely controlled by the relative reactivities of the two monomers toward the growing free radical or ion. This may be expressed quantitatively in terms of monomer reactivity ratios which are calculated from experimental copolymer composition curves using the copolymerization equation[1,2,3,4,5].

The reactivity of a monomer in copolymerization is largely dependent upon its molecular structure. The role of resonance stabilization, of polar influences, and of steric interference play a most important part in determining the reactivity of a monomer toward a free radical, a carbonium ion or a carbanion in copolymerization.

Copolymerization is an effective way of studying how different substituents on the double bond or on the carbon adjacent to the double bond govern the reactivity of the monomer toward free radicals or ions. It is important to note that these effects will be different when the monomers are competing for free radicals, cations, or anions. The contrast here was clearly brought out by Walling, Briggs, Cummings and Mayo[6]: the initial polymer formed from a 1:1 feed of styrene and methylmethacrylate may be nearly pure styrene, nearly pure methacrylate, or a 1:1 copolymer, depending upon whether the catalyst is a metal halide, an alkali metal, or a peroxide.

The free radical type of polymerization is experimentally more easily controlled, and is more readily adaptable to industrial and commercial processes and products. Because of this it has received by far the most study. Only recently, in this country and in England has the importance of ionic polymerization been realized and a concerted effort been shown in this field. The remainder of this abstract will be concerned with some of the work being carried out at The Polytechnic Institute of Brooklyn in the field of cationic polymerization and copolymerization[7].

Before quantitative or semi-quantitative copolymerization data could be properly interpreted it was necessary to study the effect of reaction variables on the monomer reactivity ratios of a typical copolymer system catalyzed by a cationic catalyst. Such data were not available. In the system styrene, p-chlorostyrene, stannic chloride, it was demonstrated that: (1) an actual copolymer is obtained, (2) the effect of dielectric constant on the monomer reactivity ratios is small,

(3) the effect of known, small amounts of water on the monomer reactivity ratios is small, (4) the effect of catalyst concentration is negligible, (5) the reactivity ratios determined at 30°, 0°, and -20° are not appreciably different[8]. Also, with the same copolymer system, no difference in monomer reactivity ratios were obtained with aluminum bromide, ferric chloride, titanium tetrachloride, stannic chloride, and titanium tetrachloride-trichloroacetic acid as catalysts[9].

The fact that the effect of the dielectric constant of the reaction medium on the reactivity ratios is small supported the idea that relative reactivities of carbonium ions derived from substituted styrenes could be determined with the aid of the copolymerization technique[10]. In particular, it was of interest to know whether the copolymerization of meta and para substituted styrenes with styrene, p-chlorostyrene, and α-methylstyrene would give information which could be correlated with the sigma constants of Hammett[11]. Some representative results for the copolymerization of styrene (M_1) with substituted styrenes (M_2) and a plot of the logarithm of the relative reactivity toward a styrene carbonium ion vs. Hammett's sigma values for these substituted styrenes are shown in Figures I and II

Fig. I

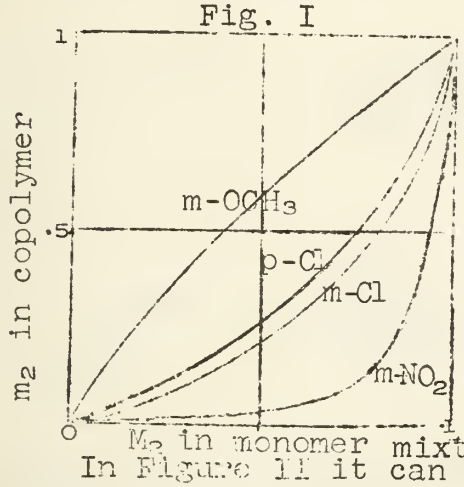
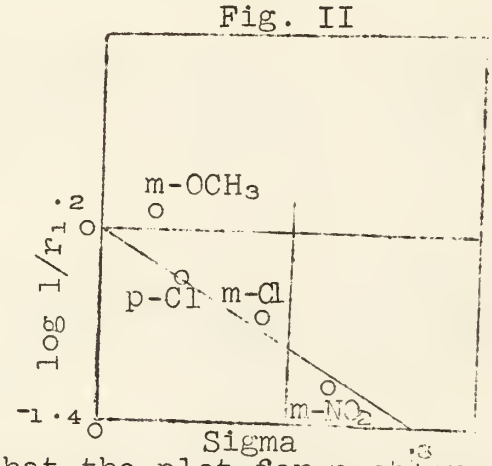


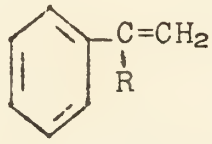
Fig. II



In Figure II it can be seen that the plot for p-chloro-, m-chloro-, and m-nitrostyrenes is a reasonably straight line. p-Methoxystyrene is so reactive that it is not recorded in the figure. The effect of molecular structure on the relative reactivity of a monomer towards a carbonium ion is well illustrated here. m-Nitrostyrene is very unreactive toward the electrophilic carbonium ion because of the strong electron-withdrawing properties of the nitro group. On the other hand, the electron-releasing properties of the methoxyl group in methoxystyrene increases the reactivity of the monomer toward such an agent. It would appear from this data and from other systems studied with different reference monomers that the monomer reactivities approximate Hammett's sigma series except for the p-methoxy and p-dimethylamino (not included here) substituted monomers. It was expected that these latter groups would not correspond to the sigma values. This question is discussed in reference 10.

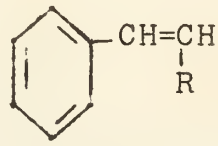
Some additional research which has recently been completed is concerned with steric effects in ionic copolymerization[12]. Alpha (A), beta (B) and para (C) alkyl substituted styrene monomers were copolymerized with a "reference monomer"

(p-chlorostyrene) and comparisons concerning the effect of size and position of these groups on monomer reactivity ratios were made.



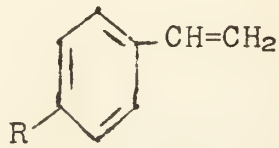
$R=CH_3, C_2H_5, n\text{-}C_3H_7$ iso-C_3H_7

(A)



$R=CH_3, C_2H_5, n\text{-}C_3H_7$

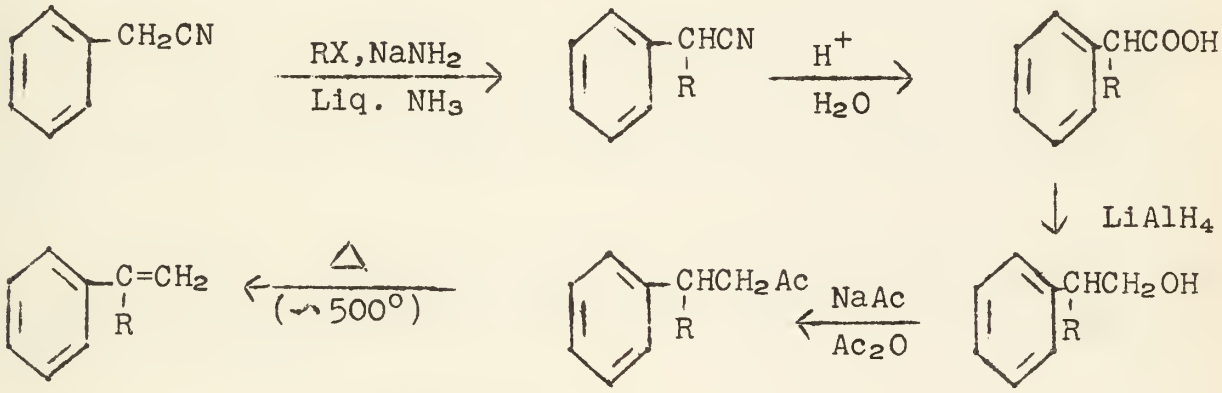
(B)



$R=CH_3, C_2H_5$

(C)

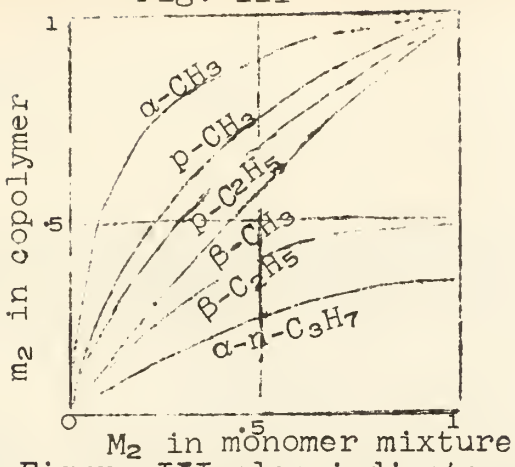
In order to obtain dependable data on steric effects, however, it was important that there were no other unknown factors influencing the reactivities of the monomers being studied. In particular, trace amounts of isomer present in the alkyl substituted styrene would lower the reactivity of the monomers, thus leading to fortuitous results. Partly on the basis of previous work on alkyl substituted butadienes[13,14] the following sequence of syntheses were chosen:



Pyrolysis of the acetates which probably proceeds through a selective cyclic mechanism yielded isomer-free products in good yields. The β-alkyl styrenes were prepared by similar procedures.

Some of the copolymer composition curves for these monomers are shown in Figure III. There are clearly two opposing factors operating here; (1) polar and resonance effects governing the reactivity of the monomer, and (2) steric interference decreasing the reactivity of the monomer. In α-methylstyrene, a 1,1-disubstituted ethylene, the electron-releasing methyl group attached directly to the double bond increases the reactivity of the monomer toward a carbonium ion. In p-methylstyrene a similar polar effect is operating, but to a lesser extent because the methyl group is further away from the reaction site. For the β-methyl case, however, steric interference begins to play a dominant role and this 1,2-disubstituted ethylene is even less reactive toward a carbonium ion than styrene.

Fig. III



The data in Figure III also indicates that when the methyl group in the beta position is lengthened by one or more methylene units, steric effects become completely dominant over polar influences and the monomer reactivity curves are greatly changed. The shape of the copolymer composition curve for this case shows that although β-methylstyrene is able to add to itself in the growing chain, this apparently is not possible for β-ethylstyrene where apparently r_2 equals zero. For the para alkyl case the situation is entirely different and steric effects are not as dominant. The reactivity of p-ethylstyrene is only slightly less than p-methylstyrene. This would be expected because the alkyl groups are further from the site of the reaction and although it is possible to transmit polar influences through the benzene ring this is not true for steric effects.

Ultraviolet absorption spectra of the side chain alkyl styrenes show interesting differences which can best be explained by some steric inhibition of resonance in the alpha substituted cases.

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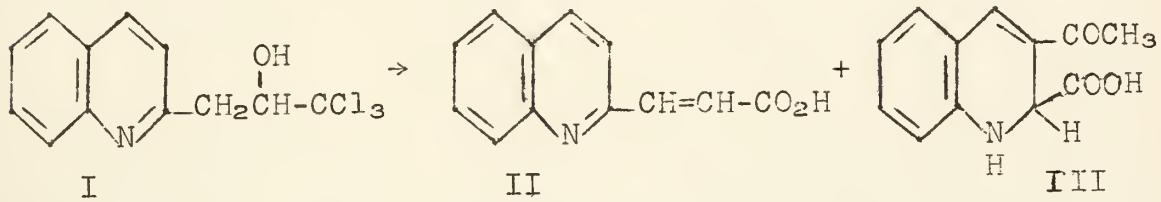
THE MECHANISM OF THE REACTION OF CHLORALQUINALDINE WITH ALKALI

Reported by Lester E. Coleman March 5, 1954

Introduction

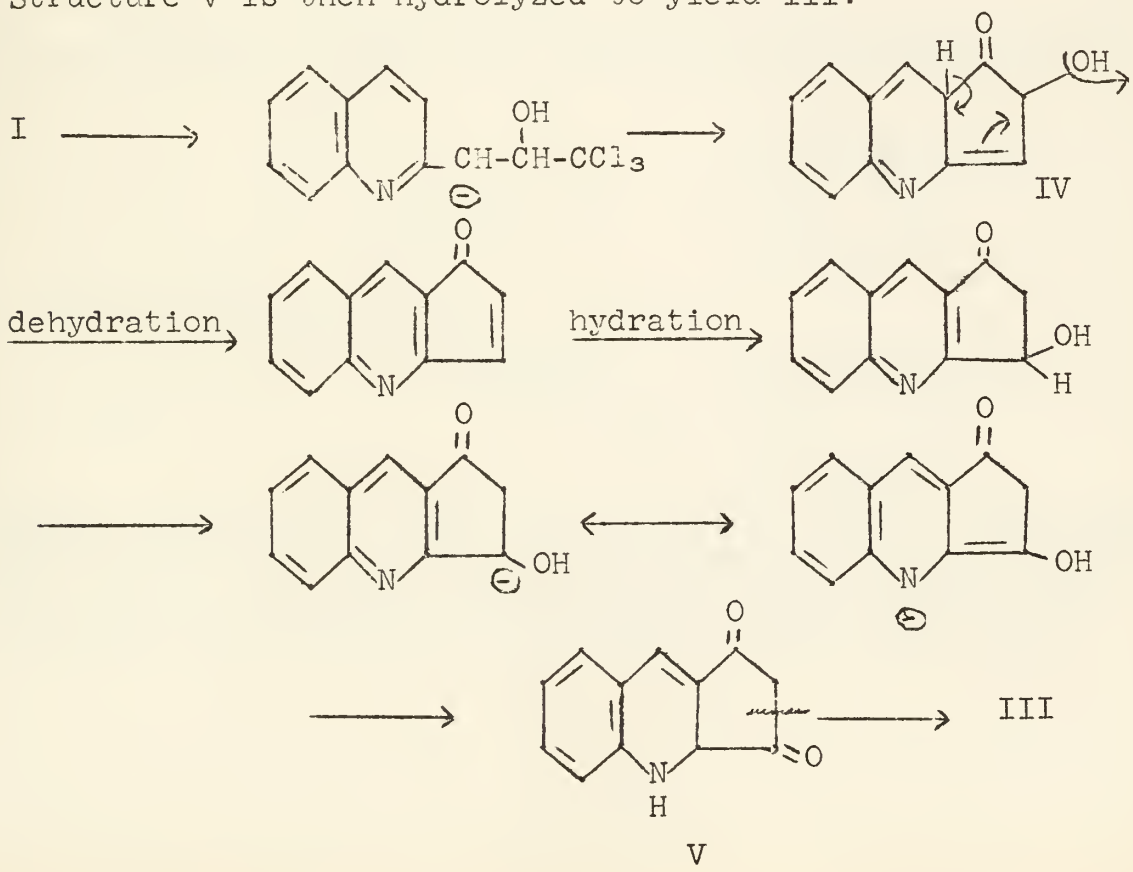
Chloralquinaldine (I) when treated with aqueous alcoholic alkali yields the expected 2-quinolylacrylic acid (II) and an orange rearrangement product, 3-acetyl-1,2-dihydroquinoline-2-carboxylic acid (III).



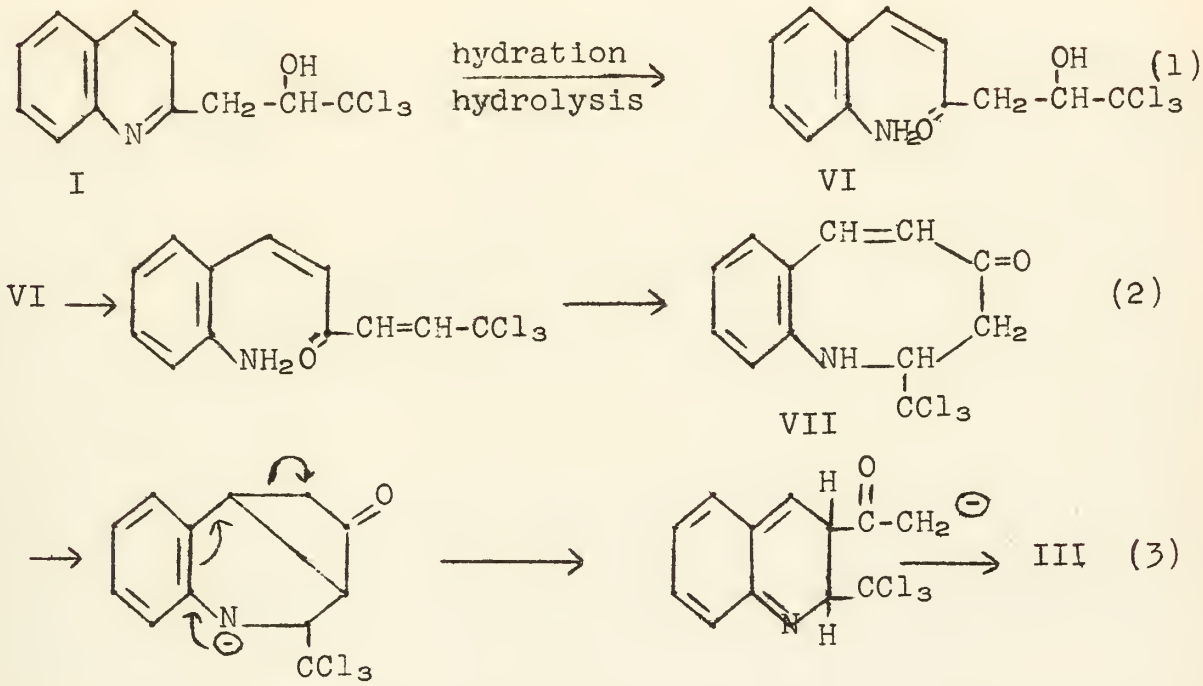
This reaction has been known for some time.[1,2,3] However, only recently the rearranged product was identified.[4] The structure proof of III has been previously discussed[7] and this report is concerned primarily with the mechanism of the reaction.

Discussion

Woodward and Kornfeld[4] have proposed a mechanism which involves formation of a carbanion at the active methylene followed by cyclization to give IV which in turn leads to V. Structure V is then hydrolyzed to yield III.

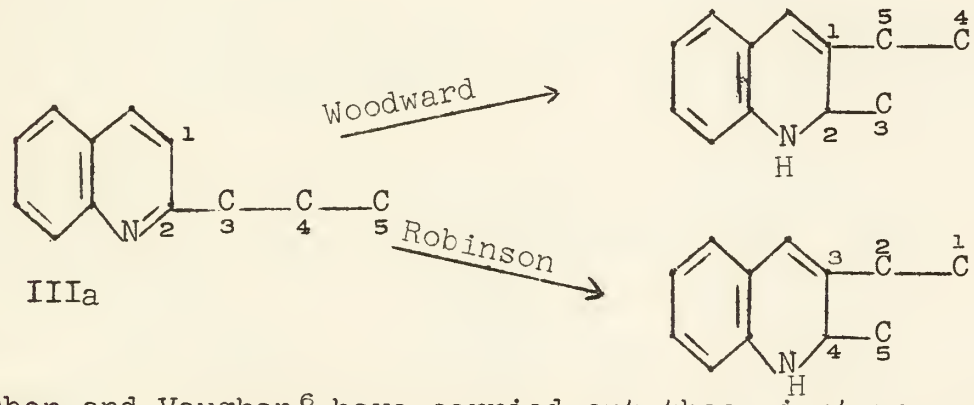


Brown, Hammick and Robinson[5] have disagreed with this mechanism and they proposed the following.



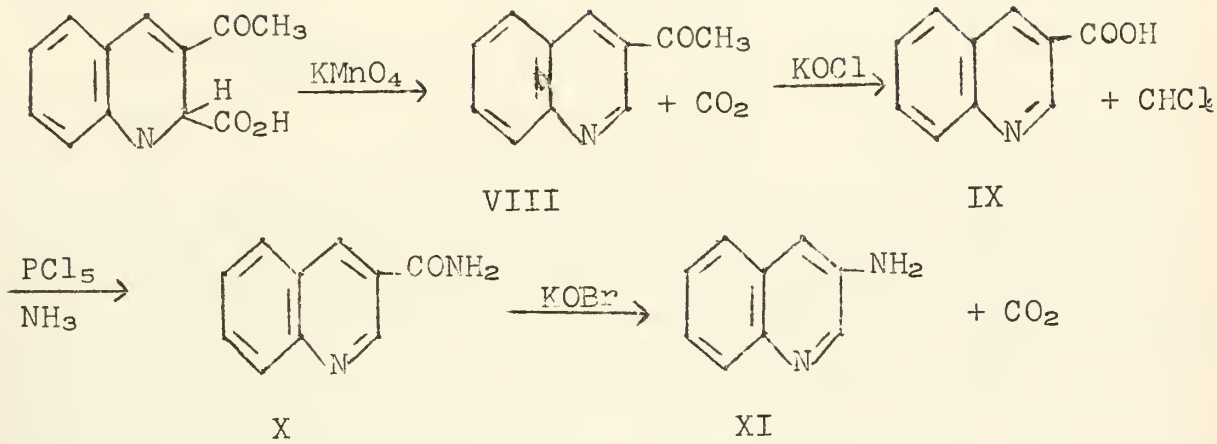
This mechanism involves a hydration followed by hydrolysis of the C-N bond to give VI. Elimination of the β-hydroxy ketone gives a α,β-unsaturated ketone which then undergoes conjugate addition of the amine in step (2). Structure VII then undergoes a Michael addition followed by ring opening and a tautomeric shift of a proton.

These two methods can be distinguished readily by the isotope method. This can be seen by the diagram below.



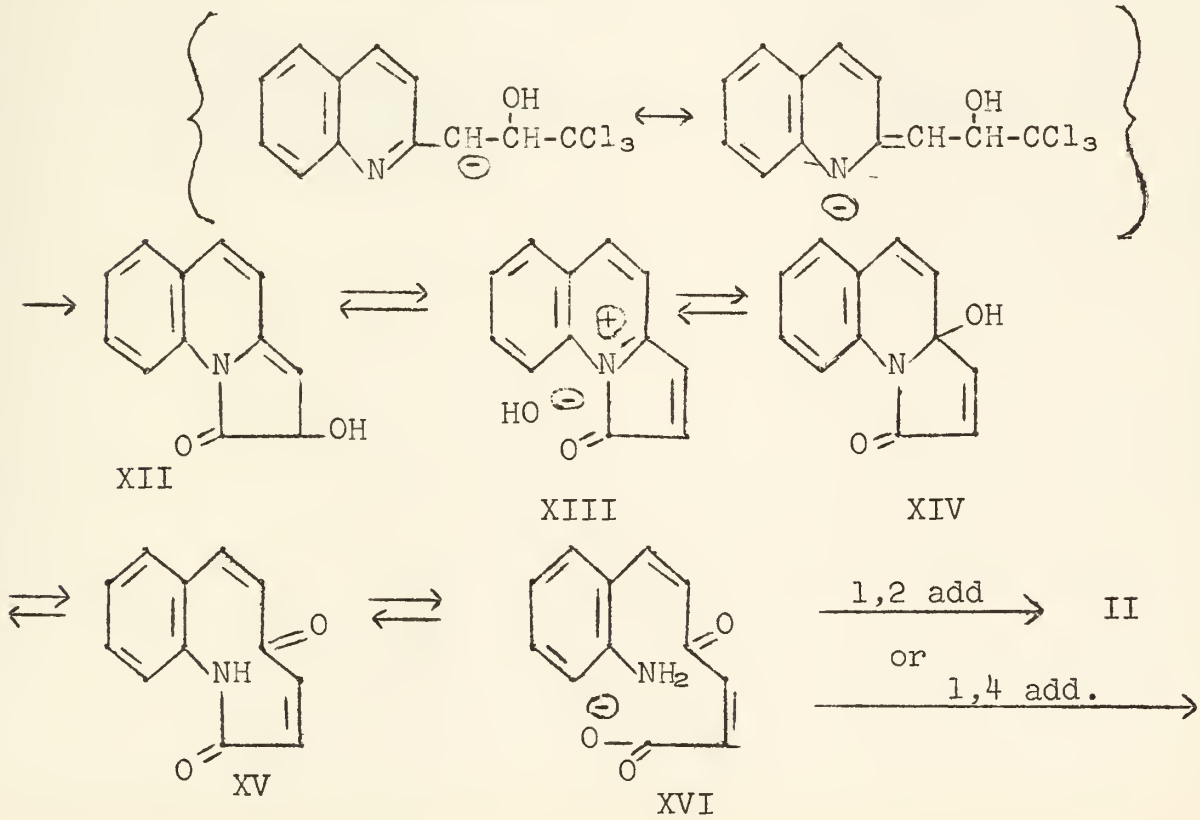
Dauben and Vaughan[6] have carried out these isotope experiments. Quinaldine with C-14 in the 3 position in IIIa was prepared and treated with alkali and the rearrangement product was isolated and subjected to the series of reactions shown

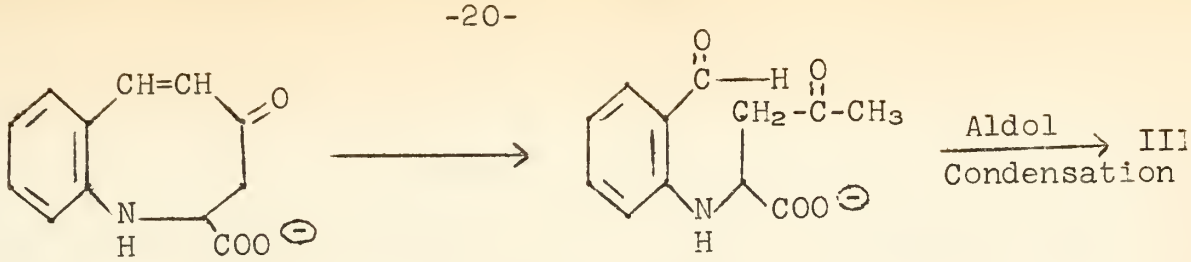
below.



The carbon dioxide formed along with VIII contained no radioactivity; the ketone exhibited the calculated specific activity. This would rule out Woodward's mechanism since the methylene is postulated to form the carboxyl group of III. Completing the reactions above, it was found that the radioactivity was contained in the aromatic nucleus.

Dauben and Vaughan then prepared quinaldine with C-14 in the 2 position of IIIa and from it prepared III. The same reactions as above were carried out and it was found that carbon dioxide from the Hofmann oxidation contained all of the radioactivity. This agrees with the mechanism proposed by Brown, Hammick and Robinson. Dauben and Vaughan, however, disagree with the intermediates postulated by Robinson and they suggested the following.





XVII XVIII

Structure XII is a vinylog of a carbinol amide and will therefore be in equilibrium with the tautomeric forms, the quaternary hydroxide XIII and pseudo base XIV which may open by hydrolysis to give XV which in turn undergoes further hydrolysis to give XVI. Structure XVI can then undergo either a 1,2 addition to give quinolylacrylic acid (II) or 1,4 addition forming XVII which undergoes a reverse aldol condensation yielding XVIII which ring closes to give III.

The primary steps in the Dauben mechanism are analogous to the reaction of quinoline when subjected to Shotten-Baumann conditions. However, it is not possible to distinguish between this mechanism and Robinson's mechanism with tracer techniques since each mechanism leads to the same change in carbon skeleton.

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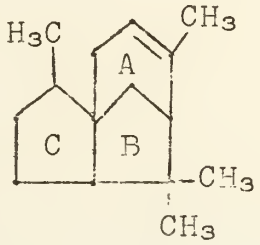
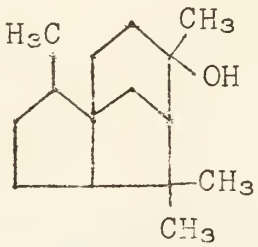
CEDRENE

Reported by Gordon R. Johnston March 5, 1954

Natural cedrene, obtained from American redcedarwood oil by fractional distillation, is a mixture of α-cedrene and β-cedrene, both tricyclic sesquiterpenes, and dicyclic sesquiterpenes of similar structure. α-Cedrene (I), $C_{15}H_{24}$, contains an endocyclic double bond, while β-cedrene has an exocyclic methylene group.



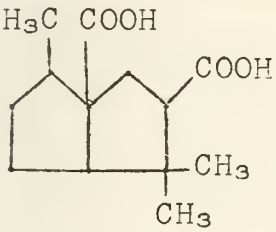
I



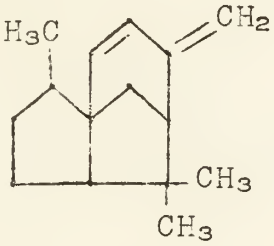
II

Since the isolation of cedrene and cedrol (II) by Walter in 1841[1] numerous investigators have conducted researches regarding the structure of cedrene (α-cedrene). Cedrene can be obtained by the distillation of natural cedrene or by the dehydration of cedrol.

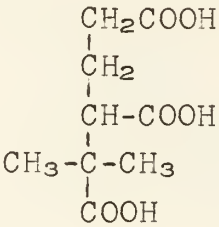
Chief among the degradation products which have led to an elucidation of the structure of cedrene are norcedrenedicarboxylic acid (III), obtained from cedrenene (IV) or cedrol, and α,α-dimethyltricarballylic acid (V).



III

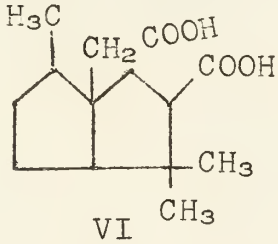


IV



V

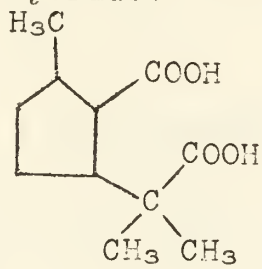
Ruzicka and Plattner[2,3] originally postulated a five-membered ring A, because cedrenedicarboxylic acid (VI) could not be cyclized to a ketone.



VI

They also disagreed with Treibs' assumption of a six-membered ring A which he based upon selenium dioxide oxidations of cedrene[4].

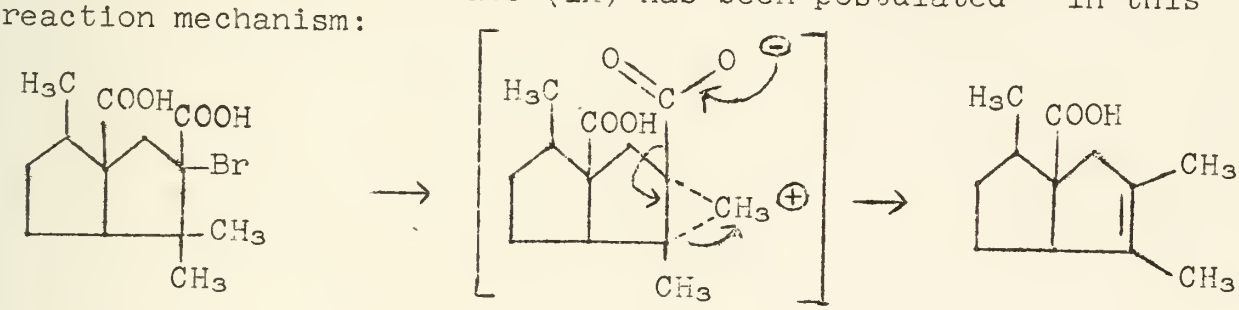
Stork and Breslow[5] have recently shown that ring A is definitely six-membered by examination of the infrared spectrum of the anhydride of norcedrenedicarboxylic acid (III). It proved to be that of a glutaric anhydride, and not of a succinic anhydride These same authors, by comparing infrared spectra, have proved ring B to be five-membered. They degraded[3] norcedrenedicarboxylic acid to a C_{11} dibasic acid (VII), whose anhydride was shown to be a substituted glutaric anhydride.



VII

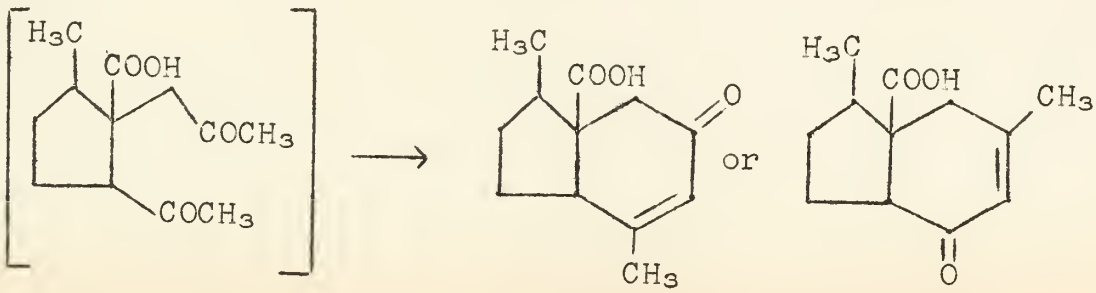
A gem-dimethyl group in ring A or ring B is shown by the isolation of α,α-dimethyltricarballylic acid (V)[6,7] from the oxidation of cedrene, bromocedrene, or norcedrenedicarboxylic acid. In a recent paper, Plattner and coworkers[8] have, by systematic degradation of dehydronorcedrenedicarboxylic acid, isolated V and proved the structure of rings B and C, thus completing the proof of structure of cedrene (I).

One rearrangement has been observed in this series[9]. When bromonorcedrenedicarboxylic acid (VIII) is reacted with base CO_2 and HBr are lost and an unsaturated bicyclic monobasic acid (X) is formed. An intermediate (IX) has been postulated[10] in this reaction mechanism:



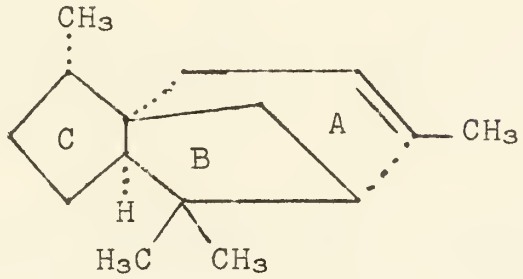
VIII IX X

Another interesting reaction is the conversion of X into XI or XII (the product has not been completely identified) by mild oxidation to the glycol with $KMnO_4$, cleavage of the glycol with lead tetraacetate, and cyclization of the diketoacid (not isolated):



XI XII

Stereochemical interpretation of the chemistry of cedrene has been put forth by Plattner and coworkers[8] who have shown the configuration of cedrene to be:



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OXIDATION OF ALCOHOLS WITH N-CHLOROSUCCINIMIDE AND TERTIARY BUTYL HYPOCHLORITE

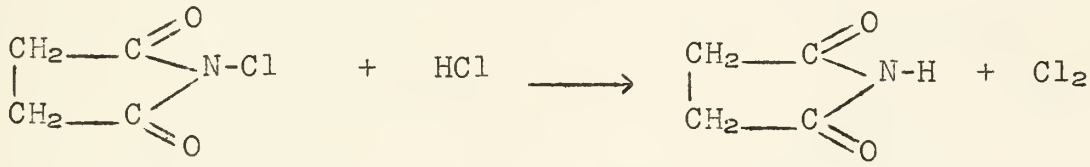
Reported by Harvey M. Loux March 12, 1954

While carrying out a study of the chlorination reactions of N-chlorosuccinimide (NCS), Hebbelynck and Martin[1] found that it also acted as an oxidizing agent. In their attempts to chlorinate benzyl alcohol and benzhydrol, they obtained, instead of the expected chlorinated products, benzaldehyde and benzophenone respectively.

Two Swiss investigators, Grob and Schmid[2,3], continued these studies of the oxidative power of NCS. They also investigated the possibility of using tertiary butyl hypochlorite (TBH) as an oxidizing agent for alcohols. In the course of their work, they found that it was equal and in many cases superior to NCS. They carried out a series of systematic studies on these two compounds and proposed mechanisms for the reactions.

The oxidizing action of these compounds has been recognized for a long time. In 1892 Seliwanow[4] reported that NCS oxidized primary and secondary but not tertiary alcohols. Tscherniac[5] proposed a mechanism which proceeded by way of a hypochlorous acid intermediate. Clark[6] found that TBH was a good chlorinating agent for most classes of compounds; however, with primary alcohols, he obtained aldehydes instead of the desired chlorinated products.

Until the recent work of Grob and Schmid, NCS and TBH were not used often as oxidizing agents because of the seeming irregularity of the reactions. Besides the expected aldehydes and ketones, esters and various chlorinated compounds were obtained. In many cases chlorine was evolved as well. These authors supposed that the chlorine arose from the reaction of the hydrochloric acid first formed with unreacted NCS or TBH, since it is well known that acid amides and alkyl hypochlorites react with hydrochloric acid to produce chlorine.

1) 

2) $(CH_3)_3\text{-}C\text{-}OCl + HCl \longrightarrow (CH_3)_3\text{-}C\text{-}OH + Cl_2$

The addition of an acid-binding agent renders the reaction more controllable and results in greatly increased yields of aldehyde or ketone. Pyridine proves most satisfactory.

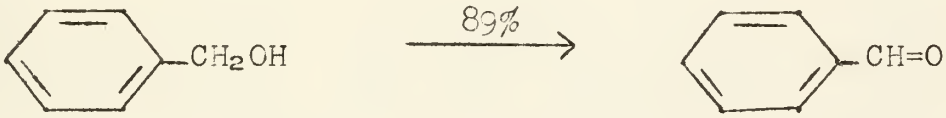
The use of NCS and TBH is limited to certain solvents; namely, those with which the oxidizing agent will not react, or if so, very slowly. As shown in table I, NCS is relatively stable in solutions of chlorobenzene, benzene, and carbon tetrachloride, in the presence of an equimolar amount of pyridine.

Table I

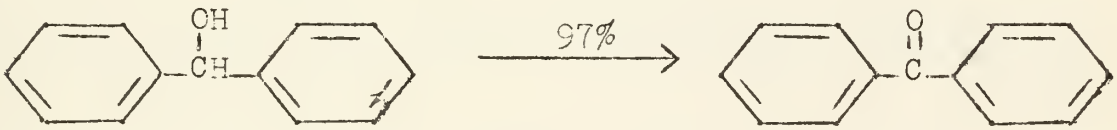
Solvent	Base	Alcohol added	Time for $\frac{1}{2}$ Decomp.
Pyridine	Pyridine	---	55 min.
Pyridine	Pyridine	Cetyl	7 min.
Dioxane	---	---	120 min.
Dioxane	Pyridine	---	25 min.
Dioxane	Pyridine	Cetyl	2 min.
Carbon tetrachloride	Pyridine	---	No dec. at 2 hrs.
Chlorobenzene	Pyridine	---	No dec. at 2 hrs.
Benzene	Pyridine	---	10% dec. at 1 hr.

The amount of carbonyl compound formed from various alcohols by the action of NCS can be determined by isolation in the free form, by isolation of the 2,4-dinitrophenylhydrazone, or by titration with hydroxylamine hydrochloride. Grob and Schmid obtained the following compounds from the respective alcohols in the yields shown:

(a)



(b)



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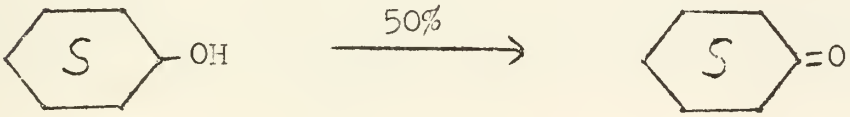

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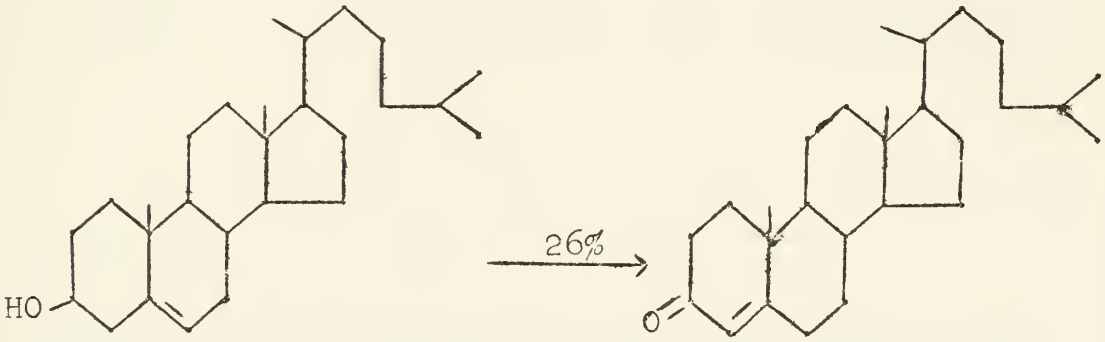


When the reaction is carried out on primary aliphatic alcohols such as normal butyl alcohol, the ester of the alcohol with the corresponding acid is obtained, but never in greater than forty percent yield.

TBH may be prepared in high yields by passing chlorine gas through a solution of tertiary butyl alcohol in aqueous sodium hydroxide.[7] Carbon tetrachloride is the best solvent for TBH in most of its oxidation reactions; however, ether may be used in cases in which the alcohol undergoes oxidation rapidly. To

the course of the reaction pyridine hydrochloride separates out and tertiary butyl alcohol is formed. Table II gives the results of the action of TBH on various alcohols in the presence of an equimolar amount of pyridine.

Table II

Alcohol	Solvent	Temperature °C.	Product	Yield %
Benzyl	CCl_4	35	Benzaldehyde	71
			Benzyl benzoate	12
Isoamyl	CCl_4	45	Isoamyl isovalerate	89
Normal hexyl	CCl_4	31	Hexyl capronate	83
Normal butyl	CCl_4	45	Butyl butyrate	66
Cyclohexyl	ether	15	Cyclohexanone	84
Cyclohexyl	CCl_4	-5	Cyclohexanone	90
α-Phenyl ethyl	CCl_4	25	Acetophenone	83
Mandelic acid	CCl_4	10	Benzaldehyde	99

With few exceptions, TBH gives significantly better yields than NCS. The reaction can be carried out at lower temperatures, probably because of the slight solubility of NCS at ordinary temperatures. (With NCS, temperatures of sixty to eighty degrees are required.) For the reaction with mandelic acid, two moles of TBH are used. The mandelic acid is oxidatively decarboxylated, giving benzaldehyde in almost quantitative yields. This may be a general method for degradation of α-hydroxy acids.

The reaction of TBH with unsaturated alcohols is not satisfactory because of the ease with which alkyl hypochlorites add to double bonds. (Upon treatment of styrene with TBH in glacial acetic acid, Hanby and Rydon[8] obtained the chlorohydrin in eighty-four percent yield.)

The mechanism of this oxidation, as proposed by Grob and Schmid, involves an initial formation of a hypochlorite which then decomposes into the carbonyl compound and hydrochloric acid.

3) $R_2\text{-CH-OH} + (CH_3)_3\text{-C-OCl} \rightleftharpoons R_2\text{-CH-OCl} + (CH_3)_3\text{-C-OH}$

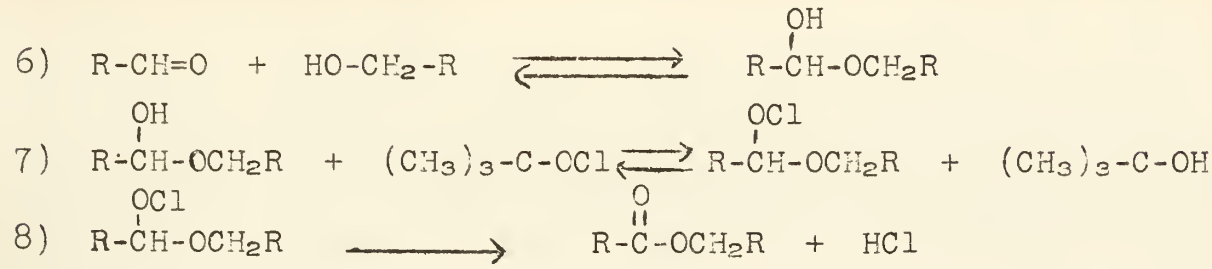
4) $R_2\text{-CH-OCl} \longrightarrow R_2\text{-C=O} + HCl$

Taylor and his coworkers[9] explained the formation of esters from primary alcohols by suggesting that the aldehyde first formed reacts with the hypochlorite intermediate.

5) $R\text{-CH=O} + R\text{-CH}_2\text{-OCl} \longrightarrow R\text{-}\overset{O}{\overset{\|}{C}}\text{-OCH}_2R + HCl$

This does not explain why only a small amount of benzyl benzoate is obtained from benzyl alcohol compared to the large amount of benzaldehyde formed; nor does it explain why the tertiary butyl ester is never obtained. Grob and Schmid made the logical assumption that the aldehyde first formed reacts

with the primary alcohol to give the hemiacetal which is then quickly oxidized by TBH to the ester.



It is known that aromatic aldehydes such as benzaldehyde possess little tendency to form acetals.[10] Since the oxidation of benzyl alcohol is a rapid reaction, hemiacetal formation does not take place to an appriciable extent. Consequently there is little or no ester formed.

The oxidation of primary alcohols to esters by such agents as chromic acid[11], chloric acid[12], and bromine[13], may also proceed by way of a hemiacetal intermediate.

The actual oxidation as shown by equation (4) might be explained in more than one way. First suggested was an ionic mechanism in which a base removes the α-hydrogen atom as a proton in the rate-determining step. This mechanism would be similar to that given by Kornblum and DeLaMare[14] for the decomposition of certain alkyl peroxides by base. Such a mechanism is not entirely justified by the results obtained thus far. Pyridine, weak base though it is, should accelerate the reaction if this ionic mechanism were correct. This is not the case. Also, the reaction may be initiated by sunlight. These facts seem to indicate that the reaction is homolytic rather than ionic, but until the course of the reaction has been studied more thoroughly, these proposals are only speculative.

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THE REACTION OF GRIGNARD REAGENTS WITH NITRILES

Reported by E. H. Hess March 12, 1954

The addition of Grignard reagents to the carbon-nitrogen triple bond followed by hydrolysis of the resulting ketimine salt is a widely used method for the synthesis of ketones. Acetophenone, for example, can be prepared in 70% yield by the addition of acetonitrile to an excess of phenylmagnesium bromide[1]. The reaction can be visualized as proceeding in the following manner:

$$CH_3CN + C_6H_5MgBr \longrightarrow CH_3\text{-}\underset{\underset{C_6H_5}{|}}{C}\text{=}NMgBr \xrightarrow{H_2O} CH_3CO\text{-}C_6H_5$$

In a like manner propiophenone can be prepared in 91% yield[1] and ω-methoxyacetophenone (from α-methoxyacetonitrile) in 78% yield[2]. The reaction, which has been extended to a wide variety of nitriles, makes possible the synthesis of many ketones. However, in this work a number of anomalous results have been encountered. It is the purpose of this seminar to discuss briefly four of these.

Reaction of the Grignard Reagent with Active Hydrogen

The principal side reaction arising when a nitrile containing an alpha hydrogen atom is treated with a Grignard reagent is that of replacement of the active hydrogen by -MgBr. When this happens a new Grignard reagent is formed which can in turn react further. Hauser and Humphlett[3] found, for example, that when phenylacetonitrile (I) was treated with methylmagnesium iodide, the normal addition product (II) was obtained in very low yield, the major product being α-phenylacetylacetonitrile (III).

$$C_6H_5CH_2CN \;\text{(I)} \xrightarrow{CH_3MgI} \begin{cases} \xrightarrow{A} \left[C_6H_5\text{-}\underset{\underset{CH_3}{|}}{C}\text{=}NMgI\right] \xrightarrow{H_2O} C_6H_5\text{-}CH_2COCH_3 \;\text{(II)} \quad 6\% \\ \xrightarrow{B} \left[C_6H_5\text{-}\underset{\underset{MgI}{|}}{CH}\text{-}CN\right] + CH_4\uparrow \end{cases}$$

Ia

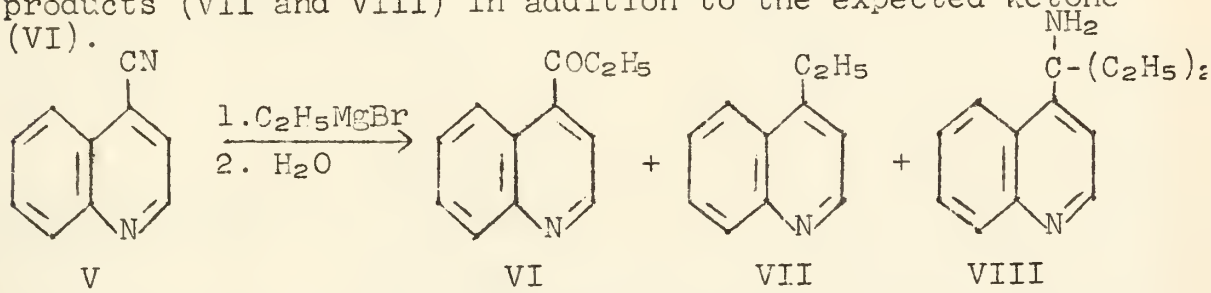
$$Ia + I \longrightarrow \left[C_6H_5\text{-}\underset{\underset{CN}{|}}{CH}\text{—}\underset{\underset{NMgI}{\|}}{C}\text{—}CH_2\text{-}C_6H_5\right] \xrightarrow{H_2O} C_6H_5\text{-}\underset{\underset{CN}{|}}{CH}\text{-}COCH_2\text{-}C_6H_5 \;\text{(III)} \quad 71\%$$

Hauser and Humphlett were able to show that steric and electronic effects could be varied in both the Grignard reagent and the nitrile so that reaction either of type A or B could be made to predominate. The preceding reaction of I with the methyl Grignard reagent illustrates the case in which attack occurs predominately at the alpha carbon atom. Conversely, if mesitylacetonitrile (IV) is treated with phenylmagnesium bromide, attack occurs only at the carbon atom of the nitrile.

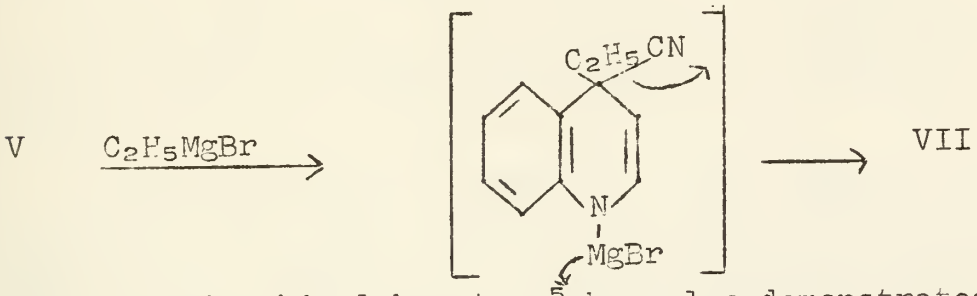
$$Mes\text{-}CH_2\text{-}CN \;\text{(IV)} \xrightarrow[2.\ H_2O]{1.\ C_6H_5MgBr} MesCH_2CO\text{-}C_6H_5$$

Displacement of Cyano by Alkyl Groups

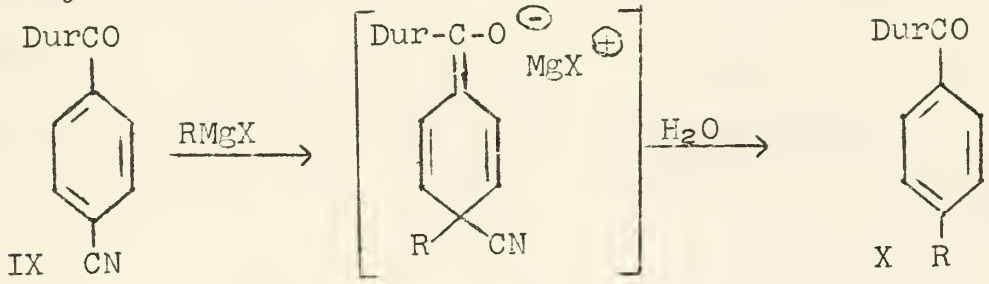
4-Cyanoquinoline (V) when treated with the ethyl Grignard reagent in 1913 by Rabe and Pasternack[4] was found to yield two products (VII and VIII) in addition to the expected ketone (VI).



The authors pointed out that the formation of VII likely resulted from a 1,4 addition of the Grignard reagent as shown below followed by a loss of cyanide ion and $MgBr^+$.



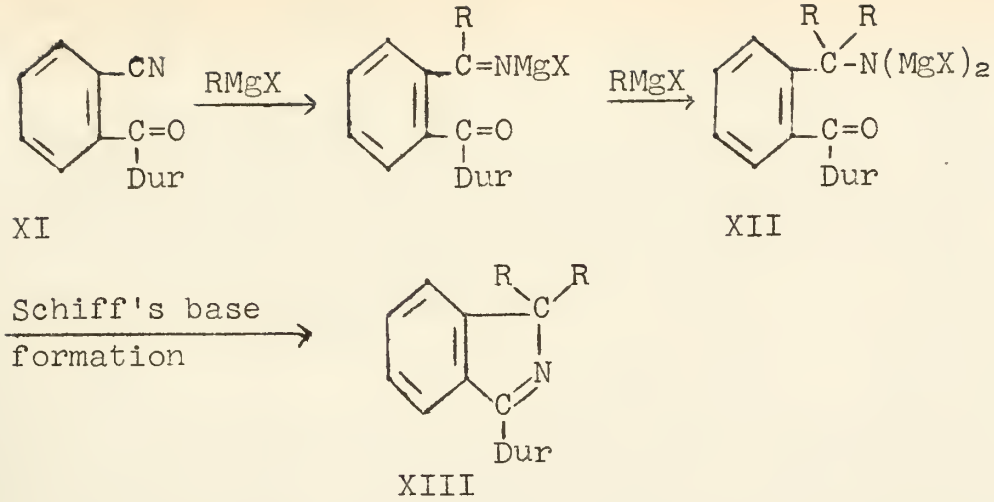
Work done in this laboratory[5] has also demonstrated this type of displacement. When p-cyanobenzoyldurene (IX) was treated with the Grignard reagent, the cyano group was displaced by the alkyl radical of the Grignard reagent to yield X.



Even though the carbonyl group of IX is hindered so that it cannot react with the Grignard reagent, it does render the para carbon atom more susceptible to nucleophilic attack than even the carbon atom of the cyano group. This activation comes about by reason of its ability to stabilize negative charge. By this reasoning then, this type of displacement would not be expected to occur with the meta isomer. When m-cyanobenzoyldurene was treated with the Grignard reagent, a high yield of the expected diketone was obtained.

Reduction of the Nitrile by the Grignard Reagent

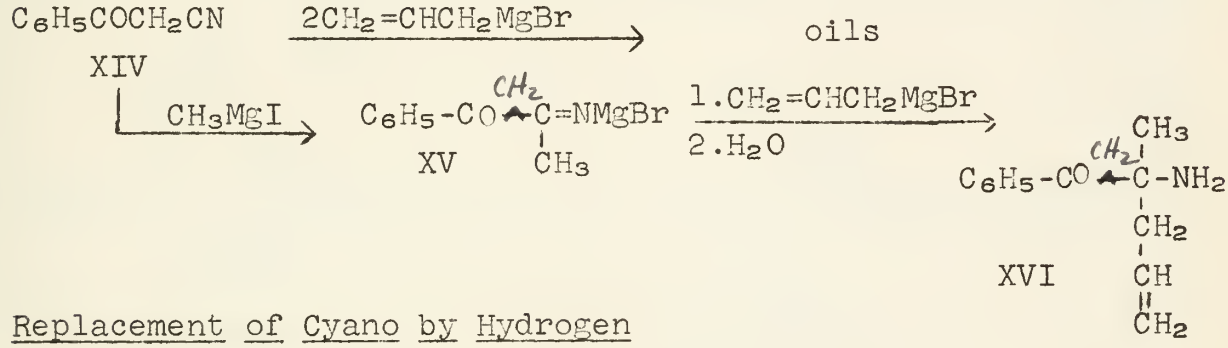
When o-cyanobenzoyldurene (XI) was treated under the same conditions, still another type of reaction was observed. The reaction did not proceed in a manner analagous to that of the para isomer, perhaps because of the difference in steric factors. The product which was formed is a derivative of a pseudoisoindole (XIII). Its formation can be explained by the following reaction mechanism:



XI XII XIII

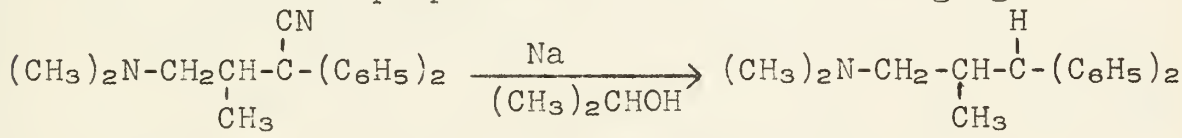
On looking back to the reaction of 4-cyanoquinoline (V) with the Grignard reagent, it should be recognized that one of the products isolated there (VIII) is likewise a reduction product as is the intermediate above (XII).

The allyl Grignard reagent has been found to act as a reducing agent on many nitriles. If benzoylacetonitrile (XIV) is treated with allylmagnesium bromide, an oil is obtained which is very sensitive to the normal purification procedures. When one mole of an alkyl Grignard reagent is added first to form the intermediate ketimine salt (XV), reduction to a crystalline amine (XVI) can be accomplished with a mole of the allyl reagent[6].



Replacement of Cyano by Hydrogen

As early as 1887 a cleavage of nitriles in the presence strong bases to produce the corresponding parent hydrocarbon was reported by Bamberger[7]. A more recent example of this displacement is that reported by Gardner, Easton and Stevens[8] in which sodium isopropoxide acts as the cleaving agent.



Since the Grignard reagent is a strong base, it is not unreasonable to expect that in some cases it may cause similar cleavages, if for some reason the cleavage takes place in preference to the other possible reactions. Examples of this are to be found in the literature as early as 1928. Lucas and Legagneur[9], in attempting to prepare triphenylmethyl benzyl ketone in the following manner, were unsuccessful and reported among other products the isolation of triphenylmethane.

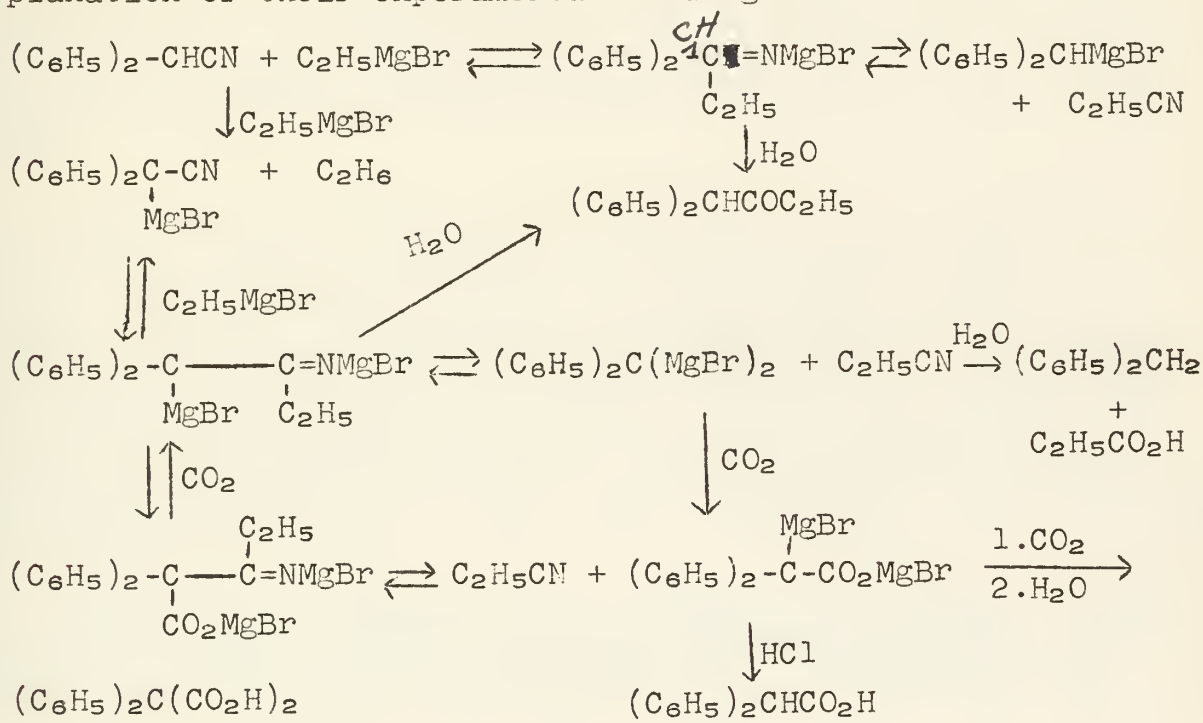
$$(C_6H_5)_3CCN \xrightarrow[2.\,H_2O]{1.\,C_6H_5CH_2MgBr} (C_6H_5)_3CH + C_6H_5CH_2CH_2C_6H_5$$

$$\not\longrightarrow (C_6H_5)_3C\text{-}COCH_2C_6H_5$$

Quite recently Blicke and Tsao[10] reported some very similar cleavages. When diphenylacetonitrile (XVII) was allowed to react with ethylmagnesium bromide, one equivalent of ethane was liberated and the following products were isolated after hydrolysis of the reaction mixture:

$$\underset{\text{XVII}}{(C_6H_5)_2CHCN} \xrightarrow[2.\,H_2O]{1.\,C_2H_5MgBr} \underset{\text{XVIII 20\%}}{(C_6H_5)_2\text{-}CHCOC_2H_5} + \underset{\text{XIX 45\%}}{(C_6H_5)_2CH_2} + C_2H_5CN$$

If, on the other hand, the same reaction mixture was carbonated before hydrolysis, diphenylmalonic acid (XX) was obtained in place of XIX. This observation is strongly indicative of the presence of a di-Grignard intermediate. The authors have therefore suggested the reaction sequence given below in explanation of their experimental findings.



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AMICETIN

Reported by Debabrata Choudhury March 19, 1954

Amicetin[1] is produced by Streptomyces vinaceus-drappus when grown in submerged culture in media containing suitable carbohydrate, organic nitrogen and mineral nutrients. The active material was separated from the filtered fermentation liquor by extraction with n-butanol at pH 8.5 to 9.5 using a Podbielniak extractor[2,3]. The amicetin rich butanol solution was extracted with dilute sulfuric acid of such strength as to give a final aqueous extract of pH 2. These operations were repeated to concentrate the antibiotic to a small volume of aqueous solution which when brought to pH 8.5 deposited the low melting crystalline form of amicetin. Further purification was affected by dissolving the crude crystals in dilute hydrochloric acid, treating with activated charcoal, precipitating the low melting crystalline form by bringing the solution to pH 8 to 8.5 and heating the aqueous slurry with stirring at 60° to 65° to convert the antibiotic to the granular, high melting crystalline form.

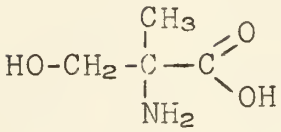
Amicetin so obtained melts at 244-45°, has a specific rotation of +116.5° (c, 0.5 in 0.1 N hydrochloric acid) and molecular formula $C_{29}H_{44}N_6O_9$. It exhibits characteristic ultraviolet absorption with a single intense maximum at 305 mμ ($E^{1\%}_{1cm}$ = 465) when dissolved in distilled water. The infrared absorption spectrum contains bands characteristic of O-H and/or N-H groups, mono substituted amide, C-O or C-O-C linkages and a substituted aromatic nucleus. Potentiometric titration of amicetin[4] indicated the presence of three ionizable groups; one was acidic with a pK'a of 10.4 and two were basic with identical PK'a values of 7.0.

Amicetin on standing at room temperature in dilute sodium hydroxide solution deposited a crystalline precipitate. It is called cytosamine and has the composition $C_{18}H_{32}N_4O_6$. Two basic groups are present having pK'a values of 3.9 and 7.0.

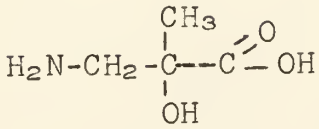
Further hydrolysis of cytosamine by heating with 6N hydrochloric acid lead to extensive decomposition. A crystalline hydrochloride was isolated from the mixture, which on treatment with dilute ammonium hydroxide yielded the crystalline free base. This compound is identified as cytosine.

Hydrolysis of amicetin with 6N hydrochloric acid at 75-80° gave another product as the hydrochloride. The base is called cytimidine and has the formula $C_{15}H_{17}N_5O_4$. This on hydrolysis gave three compounds. The least soluble of these is identified as p-aminobenzoic acid hydrochloride. The second compound obtained was shown to be cytosine hydrochloride. The third compound was found to be optically active $[\alpha]^{25}$ + 6.3 and showed the characteristics of an amino acid. pK'a values of 2.3 and 9.4 were obtained and the presence of a primary amino group was confirmed by the Van Slyke test. A Kuhn-Roth determination gave 0.5 mole of C-methyl indicating a branched chain. These facts

permit two possible structures for the amino acid I and II.



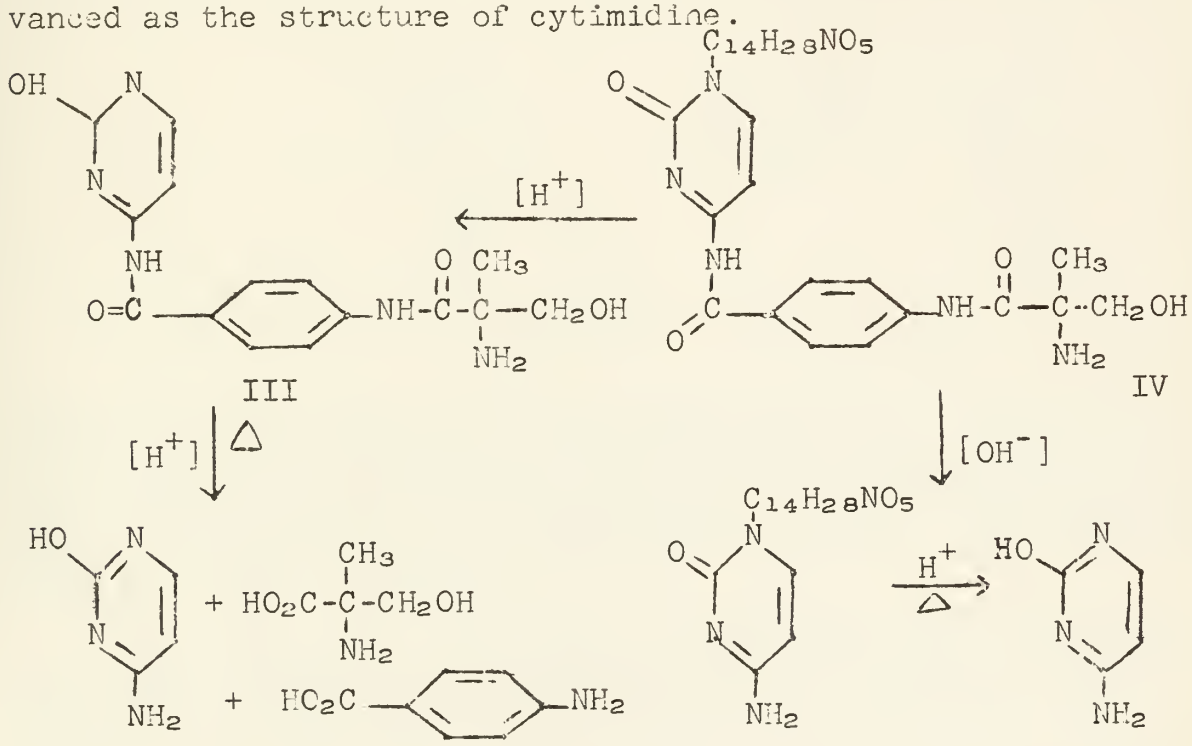
I



II

In the Van Slyke ninhydrin reaction no CO_2 was formed. This fact favors II as the likely structure. However, it has been reported that α-methyl α-amino acids behave abnormally in this reaction[5]. To distinguish between these two structures DL-α-methylserine I and DL-α-methylisoserine were compared with the amino acid obtained from amicetine. Results obtained from infrared spectra are inadequate to rule out either of these two possibilities. However, potentiometric titration showed that DL-I has two pK'a values of 2.3 and 9.4. The pK'a values for DL-II were 2.7 and 9.15. Since the unknown amino acid gave pK'a values of 2.3 and 9.46, it is believed that the amino acid in amicetin is dextro-α-methylserine I.

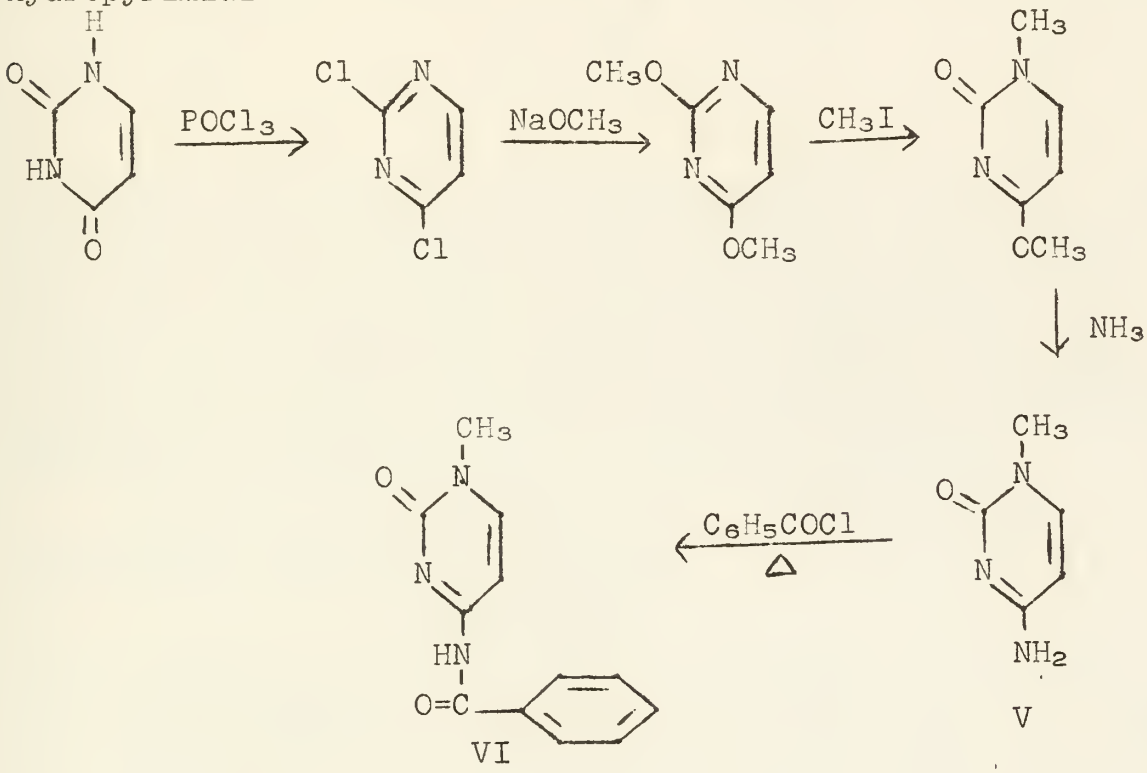
Cytimidine, $C_{15}H_{17}N_5O_4$, consists of three components, cytosine, p-aminobenzoic acid and dextro-α-methylserine. The linkages are deduced from the following facts. Potentiometric titration of cytimidine indicated two ionizable groups, one is acidic with a pK'a of 9.8 and the second is basic with a pK'a of 6.9. Since no free carboxyl was present it is concluded that the carboxyl groups of p-aminobenzoic acid and dextro-α-methylserine are involved in amide linkages. A negative Bratton-Marshall test showed that the amino group of p-aminobenzoic acid is bound. On the basis of these facts III is advanced as the structure of cytimidine.



The known properties of amicetin and the structural features of cytosamine and cytimidine allow the partial structure IV for amicetin.

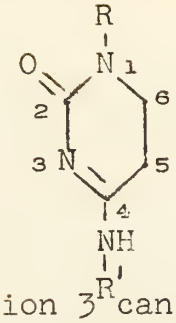
These linkages require further consideration. A titration of the reaction mixture, obtained by mild alkaline hydrolysis of amicetin showed that two basic groups (pK'a values of 7) of amicetin were unaffected but the weakly acidic group with pK'a 10.4 disappeared. At the same time a new basic group pK'a 3.8 and acidic group (pK'a 3.9) were formed. Cytosamine contains two basic groups with pK'a values of 3.9 and 7.0, therefore, the remainder of the molecule must contain the acidic group and the other basic function. These changes are consistent with a hydrolysis which involves splitting of the cytosine p-aminobenzoic acid linkage. The acidic pK'a 10.4 group destroyed in the hydrolysis is apparently the amide linkage between cytosine and the p-aminobenzoic acid moiety.

Since the acidity of the -NH group of this cytosine p-aminobenzoic acid linkage was unexpected it was compared with a suitable model compound, 1 methyl-2-keto-4-benzamido-1,2-dihydropyrimidine.



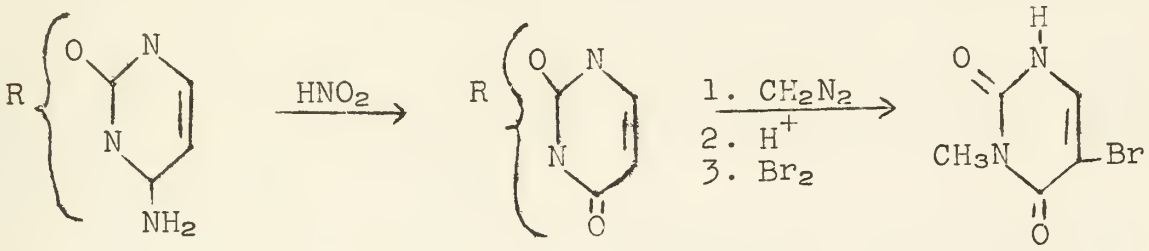
Titration of V showed one basic group, pK'a 4.5. However, VI had one weakley acidic group with pK'a of 10.6. When allowed to stand in 0.1 N sodium hydroxide for 18 hours the pK'a 10.6 group disappeared and the basic group of 1 methyl cytosine and the carboxyl of the benzoic acid were titrable. This behavior parallels that of amicetin.

The acid-labile bond which is hydrolyzed when cytimidine is formed requires further consideration. Becasue of acid lability the three likely points of attachment to the cytosine moiety are through the ring nitrogens or the phenolic hydroxyl at 2.



$R = C_{14}H_{28}NO_5$

Attachment at position 3 can be excluded by the following information. Cytosine on treatment with nitrous acid removes the 4 amino group of the cytosine nucleus. The resulting uracil derivative was then treated with diazomethane, hydrolyzed and 3-methyl uracil was isolated as the 5-bromo derivative VII.



VII

Attachment at position 2 can be excluded by two facts. First cytosine does not reduce Fehling's solution. It is also believed that the oxygen in the 2 position must be fixed in the keto form to provide the acidic NH group present in amicetin and in the model compound VI. Support for this belief comes from the fact that N-benzoyl cytosine has only one acidic group which is attributed to the phenolic hydroxyl at position 2. It is, therefore, seems most likely that $C_{14}H_{28}NO_5$ grouping is attached to the 1 position of cytosine.

Studies on the remainder of the amicetin molecule ($C_{14}H_{28}NO_5$) are still in progress.

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THE S_N2' REACTION

Reported by Richard E. Lyle March 19, 1954

The S_N2' reaction was first postulated by E. D. Hughes[1] as a bimolecular reaction involving attack at the γ-position of an allylic system by a nucleophilic reagent:

$$Y^- + CHR'{=}CHCHRX \longrightarrow YCHR'CH{=}CHR + X^-$$

Early attempts to realize the reaction failed, however. A. G. Catchpole and E. D. Hughes[2,3] could not detect the reaction when α-methylallyl chloride or γ-methylallyl chloride was treated with sodium ethoxide in ethanol. When small amounts of ethoxide were present, S_N1 reactions were observed, and the same mixture of products was obtained with either chloride. When large amounts of ethoxide were used, bimolecular reactions were obtained, but the products were those of the normal S_N2 reactions. Young and co-workers[4,5] found that when the same chlorides were converted to acetates by second order reactions with potassium acetate in acetic anhydride or tetraethylammonium acetate in acetone only the acetates from normal S_N2 reactions were obtained.

Carroll[6,7] reported that α-phenylallyl alcohol and cinnamyl alcohol, when treated with ethyl acetoacetate and basic catalysts, were converted through the corresponding esters to cinnamylacetone and α-phenylallylacetone, respectively. That these reactions were S_N2' was later suggested[8], but Cope[9] found that the products were formed by successive ester interchange and cyclic rearrangement of the unsaturated esters.

Bergmann[10] reported that α,γ-dimethylallyl chloride completely loses its optical activity when it is treated with sodiomalonic ester or sodium diphenylmethide. Since the same product results from either S_N2 or S_N2' mechanism and since steric complications can enter into the latter, the exact mechanism cannot be determined from the product alone.

Because of the early failures in realizing the S_N2' reaction, Hughes and Ingold[11] postulated that "Mechanism S_N2' is not normally available as a route for anionotropic change." They argued that nucleophilic attack at the γ-position would be hindered by the presence of the π-electron cloud around the positive nucleus. The argument was based on comparison with nucleophilic attack at an isolated double bond. Winstein, however, has asserted that the comparision ought to be made rather with nucleophilic attack at a double bond conjugated with an electron withdrawing group.

Dewar[12] has rejected the availability of the S_N2' reaction on grounds that its transition state must be linear, and, therefore, its entropy and frequency factor must be low. Also, "The transition state contains two normal bonds less than the initial state, and its energy of formation should therefore be much higher than that of a normal S_2 transition state where one bond only is broken." Winstein and Young[13] have proposed, however, an alternative angular transition state as will be shown later in the abstract.

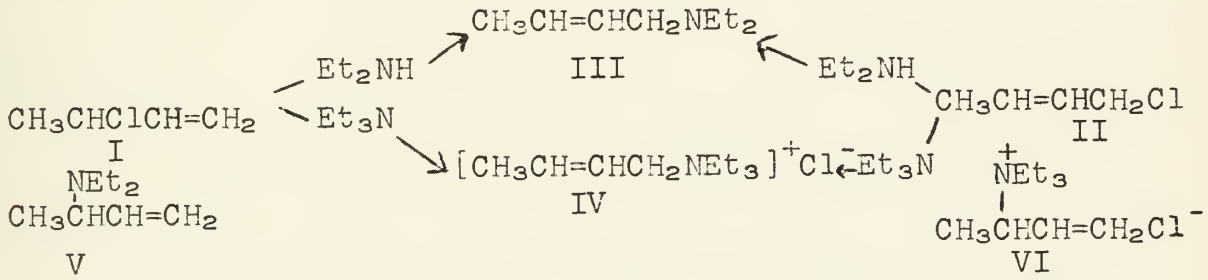
In spite of the theoretical doubts, however, many instances of S_N2' reaction have been found. In general the reactions are indeed slower than the corresponding S_N2 reactions.

Nevertheless, they are easily attainable, and simple techniques have been used to emphasize S_N2' at the expense of S_N2: first, if Y differs from X only in being radioactive, then S_N2 reaction regenerates starting material, and the S_N2' can continue though slowly, to completion; second, R may be altered to hinder the S_N2 reaction; third, R may be altered to favor S_N2' electronically; and, fourth, Y can be changed to favor S_N2'.

Winstein, Young, and Kepner[14] first reported a convincing demonstration of the S_N2' reaction. They found that whereas the primary chlorides, γ-methyl and γ-ethylallyl chloride, gave less than 1% S_N2' products, the corresponding secondary chlorides, α-methyl and α-ethylallyl chloride, both underwent the S_N2' process, the former in 10% yield in refluxing ethanol and 6% yield at room temperature, the latter in 23% yield. The starting materials were carefully purified to insure that the products of the reaction did not arise from impurities. The possibilities of thermal rearrangement or solvolysis leading to the products were eliminated when it was found that the chlorides were stable under the conditions employed and that the reaction kinetics were second order-the first order solvolysis being so slow as to be negligible.

Dewar[15] has objected to the S_N2' classification here, however, and has postulated that the reaction could involve O-alkylation followed by a Claisen type rearrangement. Winstein, however, has pointed out that the O-alkylation product would be a ketene acetal, which, though it might be expected to rearrange to C-alkylated product in a non-hydroxylic environment, would probably be converted to an ortho ester in the ethanolic solution used. Also, O-alkylation with malonic esters is far from prevalent.

The reactions of butenyl chlorides with diethylamine has been shown to follow the S_N2' mechanism. The reactions with triethylamine have been shown to yield S_N2' products, but their modes of origin are ambiguous.[13]



It was found that both I and II gave the same product with diethylamine with or without solvent. II was converted to III in 85% yield when the reagents were allowed to stand at room temperature for two days. I was converted to III when the halogen and the amine were refluxed for thirty-six hours. I gave no V under the conditions employed. With triethylamine II was converted to IV in 74% yield after refluxing in benzene solution for two days. I was converted to IV after thirteen days of refluxing. Since the S_N2' products could have arisen from either a rearrangement of I prior to substitution or from rearrangement of initially formed normal products, V or VI, these possibilities were investigated. Both I and V were shown to be stable in the cases of reaction with diethylamine. With triethylamine, however, both the starting chloride and the S_N2 product, VI, were found to be unstable under the reaction

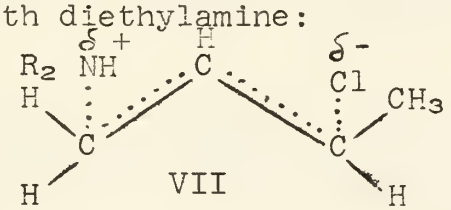
conditions employed. Thus only the case with diethylamine was considered by the investigators as definitely S_N2'.

The kinetics of the reaction of I with diethylamine were second order provided that it was considered that two moles of diethylamine reacted for each mole of chloride that reacted. This can be accounted for by the relative basicities of III and diethylamine and their relative solubilities in the reaction medium.

$$Et_2NH + CH_2{=}CHCHClCH_3 \longrightarrow [Et_2NHCH_2CH{=}CHCH_3]^+ + Cl^-$$

$$[Et_2NHCH_2CH{=}CHCH_3]^+ + Et_2NH \longrightarrow Et_2NH_2^+ + Et_2NCH_2CH{=}CHCH_3$$

Young and Winstein[13] have proposed a non-linear transition state (VII) with entering and leaving groups cis for the reaction of I with diethylamine:



VII

This transition state would accommodate a cyclic mechanism involving hydrogen bonding between the amine hydrogen and the leaving chlorine atom. Such a mechanism has been proposed by Hughes and Ingold in lieu of the S_N2' hypothesis.[16]

The failure of I and triethylamine to undergo unambiguous S_N2' reaction would seem to indicate that the amine hydrogen is a prerequisite for the reaction. However, in later work Young was able to realize a bimolecular reaction between trimethylamine and I in acetone.[17] Both S_N2 and S_N2' products were isolated under conditions wherein no rearrangements of products or starting materials occurred.

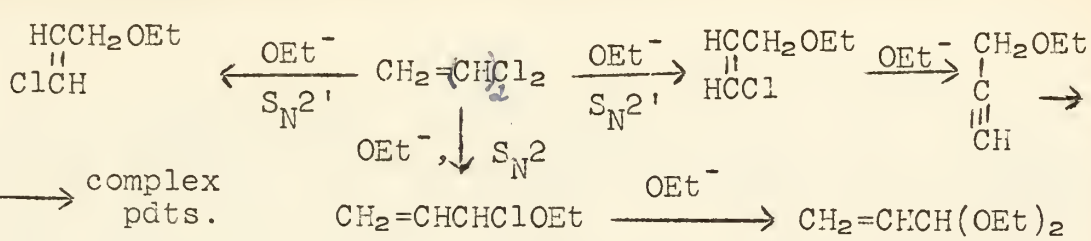
Winstein and Young use the arguments of the above-mentioned hydrogen bonding and the attraction of the unlike charges developed at the ends of the system as the basis for their cis arrangement of entering and leaving groups. It must be noted that both S_N2' reactions involving no hydrogen bonding and negative charges on both the entering and leaving groups have been realized. Also, an analogy can be drawn between the S_N2' transition state and a bimolecular elimination transition state where the entering and leaving group are oppositely charged. Thus, for the time being, cis substitution must be regarded as questionable.

England and Hughes[18] have elucidated a reaction which is a particularly clear example of type S_N2' in the attack of radiobromide ion on α- and γ-methylallyl bromides. Here, the use of isotopes has enabled them to detect a much slower S_N2' reaction which is almost completely masked by an S_N2 reaction.

Bromide	Reaction	10^6k_2 (25°)	$Log_{10}A_2$	E_A
α-methylallyl	S_N2	879	9.06	16.5
	S_N2'	14.9	9.40	19.4
crotyl	S_N2	141,000	9.93	14.7
	S_N2'	5	~9	19

Recently, De La Mare and Vernon have investigated the following series of S_N2' reactions:

1.[19]



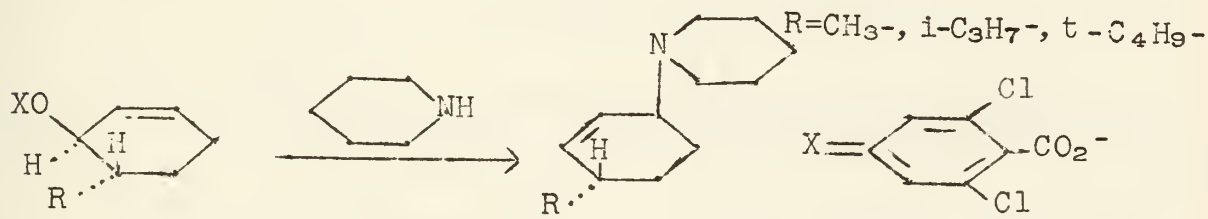
2.[20] $CH_2{=}CHCHCl_2 + C_6H_5S^- \xrightarrow[38\%]{S_N2'} C_6H_5SCH_2CH{=}CHCl$

Here, cis and trans isomers were produced in almost equal amounts. This is consistent with either cis or trans transition states, however.

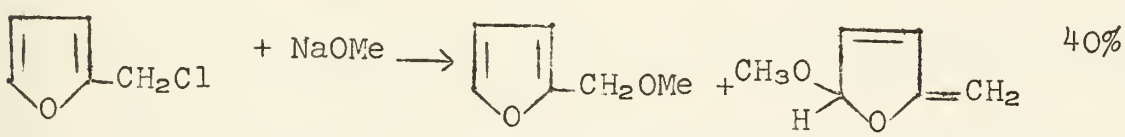
3.[21] $CCl_3C(CH_3){=}CH_2 + NaSC_6H_5 \xrightarrow{EtOH} CCl_2{=}C(CH_3)CH_2SC_6H_5$

4.[22] $CH_2{=}CHCMe_2Cl + C_6H_5S^- \longrightarrow C_6H_5SCH_2CH{=}CMe_2$

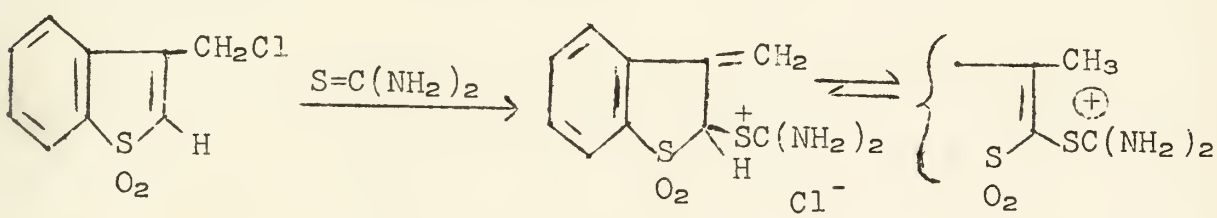
Stork[23] has shown that in the cyclohexene system the entering group comes in cis to the leaving group by the following reactions:

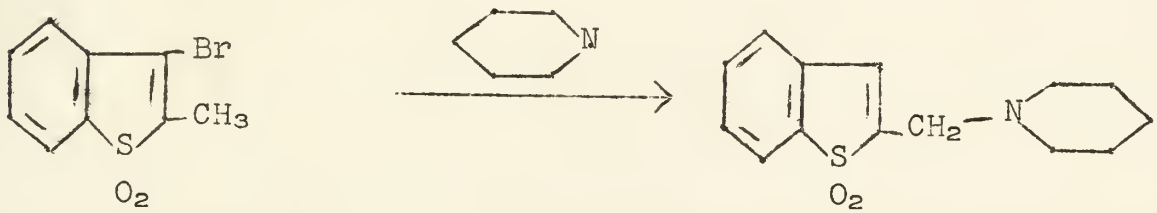


A pseudo-S_N2' reaction has been found in an abnormal reaction of α-chloromethylfuran with sodium methoxide.[24]



Bordwell and Weinstock[25] have found S_N2' reactions in the benzothiophene 1,1-dioxide series.





The latter reaction is considered to proceed via a base catalyzed tautomerism followed by an S_N2' displacement.

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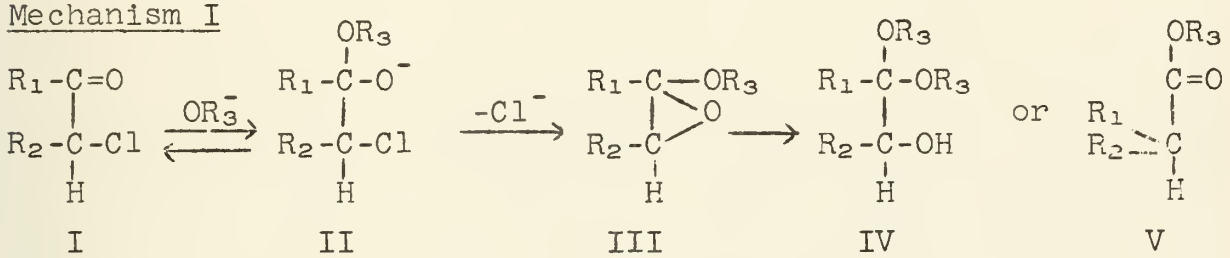
The Alkaline Rearrangement of α-Halo Ketones

Reported by Hugh H. Gibbs March 26, 1954

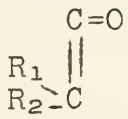
Ever since Faworskii[1] discovered in 1894 that α-halo ketones could be converted by the action of base into carboxylic acids with the same number of carbon atoms considerable effort has been expended in elucidating the mechanism of this reaction. Depending on whether the base is hydroxide ion, alkoxide ion, or amine, the product is an acid salt, ester, or amide. Generally there is a constant production of hydroxy ketone or its ketal. This seminar reviews the various mechanisms which have been proposed.

Mechanism I



I II III IV V

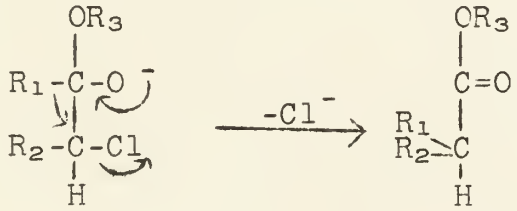
This mechanism was proposed by Faworskii[2] and later Aston[3]. The epoxide-ether type of structure has been isolated by Temnikova[4] and Stevens[5] in their studies on α-bromopropiophenone. Although the conversion of III to IV is not unexpected, the path by which III could become V is not apparent. Indeed, Stevens could obtain no evidence for rearrangement of his epoxide-ether to acid or ester.



VI

Richard[6] suggested the intermediate formation of a ketene derivative VI by elimination of hydrogen chloride from the enol of I (mechanism II) or by elimination of hydrogen chloride from I by a process analogous to the Hofmann rearrangement (mechanism III). The chief evidence was a transient color and the presence of a ketene dimer in the products. However, examples of the rearrangement are known in which the formation of a ketene dimer is impossible.

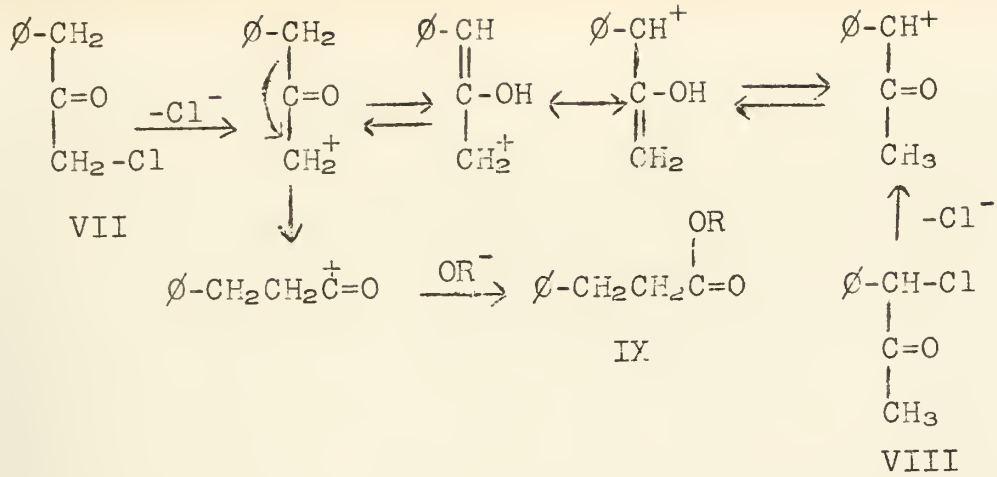
Mechanism IV



This mechanism has received some favor as it is closely analogous to the well established course of the benzilic acid rearrangement.

Now, mechanisms I to IV all predict that the carbon to which the chlorine is initially attached will become the α-carbon of the carboxylic acid. Since this is not the case, Richard[7] proposed a chlorine migration from α- to the α'-carbon atom.

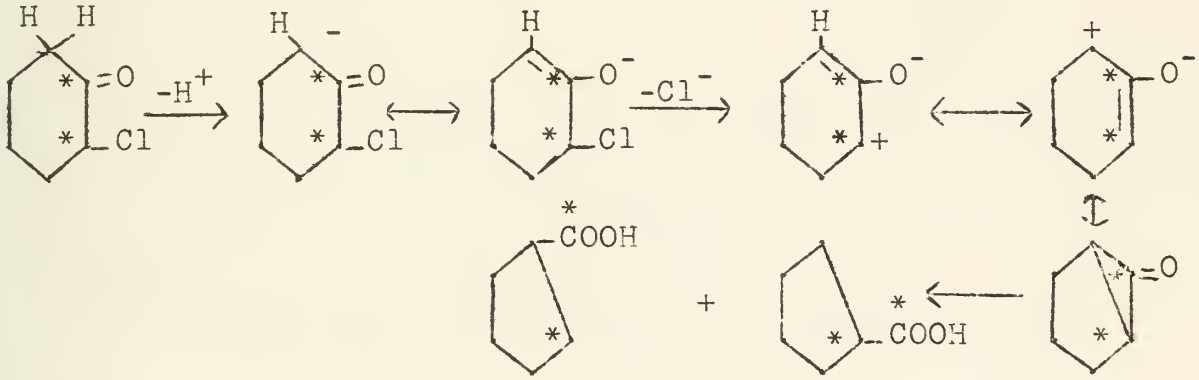
Mechanism V



McPhee and Klingsberg[8] extended Richard's work with α-phenyl-α'-chloroacetone (VII) and α-phenyl-α-chloroacetone (VIII). Both give β-phenyl propionic ester (IX). Discounting halogen migration they suggested mechanism V which provides a common intermediate leading to a single product. This mechanism does not seem probable, however, as it does not give an important enough role to the base which is essential to the reaction.

Mechanism VI

Loftfield[9,10] using α-chlorocyclohexanone as a model compound whose substitution and steric factors do not preclude any of the mechanisms so far considered has proposed the following cyclopropanone mechanism (VI).



Starting with labelled α-chlorocyclohexanone in which the C^{14}-atoms were equally distributed between the carbonyl and α-carbon atoms, he found that the position of the radioactivity was unchanged in the recovered α-chlorocyclohexanone whereas it was equally divided between the α- and β-positions of the product acid. This indicated that there had been no halogen migration and that the only mechanism which so far could account for the results was the one involving the cyclopropanone intermediate.

It must be noted that the substitution and rearrangement products are not derived from a common intermediate. The former is derived by base attack at the carbonyl carbon while the latter at the α'-hydrogen.

Loftfield[11] has recently studied the effect on the rearrangement of changing halogen using halomethyl cyclohexyl ketones as examples. He reasoned that the less electronegative the halogen, the more readily an epoxide ring would form and so the greater the chance for substitution to take place rather than rearrangement. In analogy to the work of McCabe and Warner[12] on the ring closure of ethylene halohydrin anions to ethylene oxide he hoped that the rate of substitution might be changed by a large factor while the rate of rearrangement was substantially constant. This prediction was confirmed in the case of the bromo- and chloromethyl cyclohexyl ketones. Attempts to make the fluoro compound failed. The results of these experiments were not entirely compatible with the cyclopropanone mechanism as both possible product acids could not be isolated from the reaction mixture nor was there any evidence that more than one isomeric acid was present.

It is also apparent that the cyclopropanone mechanism cannot be applied to the rearrangement of all α-haloketones. In some cases where there is no α'-hydrogen rearrangements still take place.

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THE CONFIGURATION OF SCOPOLAMINE AND VALEROIDINE

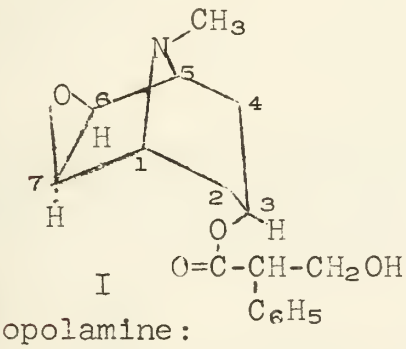
Reported by Melvin J. Gortatowski March 26, 1954

Introduction:

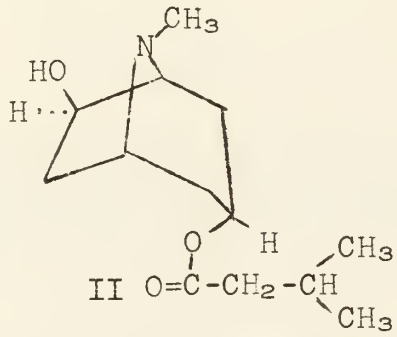
Scopolamine, the major alkaloid of Datura Metel, and valeroidine, a minor alkaloid of Duboisia myoporoides, both belong to the tropane group of naturally occurring bases. The structure of scopolamine has been known for some time and its elucidation summarized by Holmes[1]. As early as 1923, Willstätter[2] proposed four possible configurations of scopolamine, but no choice between them was made. The structure of valeroidine was uncertain until recently.

The reason for the uncertainty of the configuration of scopolamine and structure of valeroidine was that these bases unlike some others of the tropane group, namely atropine and cocaine, could not be hydrolyzed to the well-known tropines and ecgonines.

The presently accepted structures for scopolamine (I) and valeroidine (II) are:



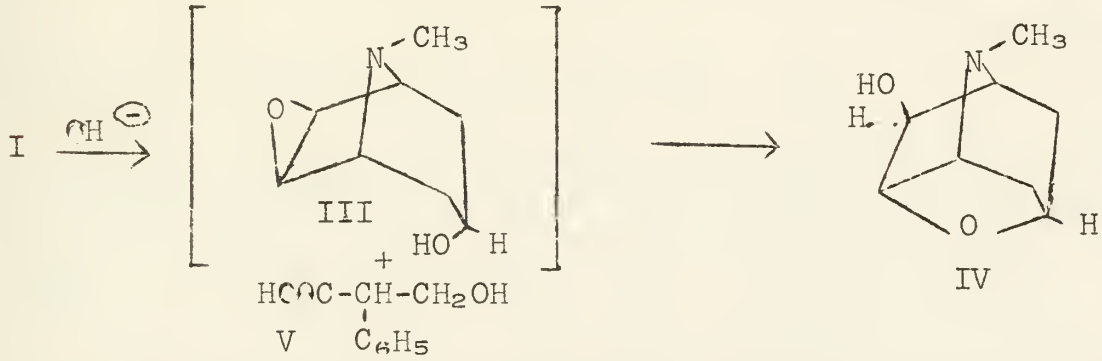
I



II

Scopolamine:

Configuration of C_3:- Alkaline hydrolysis transforms scopolamine (I) to scopoline (IV), a tetrahydrofuran derivative, presumably through the intermediate scopine (III). The scopine (III) can be isolated if the hydrolysis is carried out using

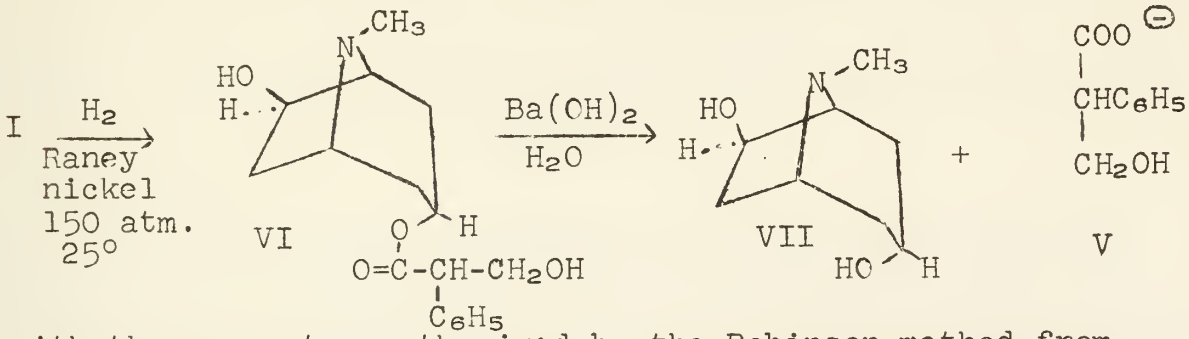


the enzyme pancreatic lipase in a buffered solution. There is obtained together with the optically inactive scopine (III), the levorotatory tropic acid (V) the configuration of which has not yet been determined. Treatment of scopine with acid or base converts it to scopoline (IV)[2]. This ready conversion has led Fodor[3,4,5] to suggest that the rearrangement involves a nucleophilic backside attack by the C_3-oxygen atom on the $C_{6,7}$-epoxide ring. ψ-Scopine, the C_3-epimer of scopine (III), does not exhibit the conversion to scopoline (IV) under the same conditions. The rearrangement appears most feasible if the

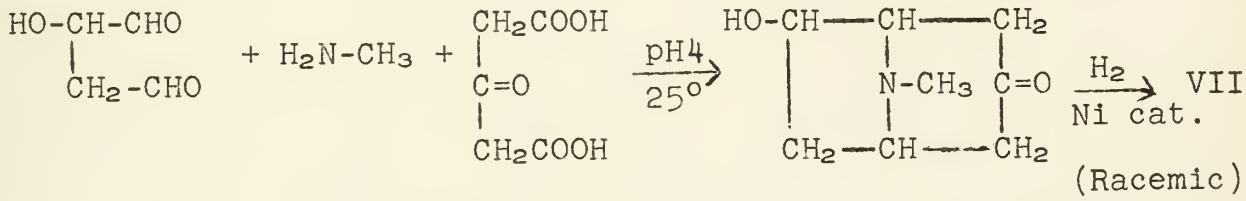
C_3-hydroxyl of scopine (III) is α- and the 6,7-epoxide ring β- with respect to the $>N-CH_3$ bridge*.

Configuration of the 6,7-epoxide ring:- Perhaps the best evidence for the β-configuration of the epoxide ring arises from the correlation of scopolamine (I) with valeroidine (II) in which the β-configuration of the C_6-hydroxyl group has been established (see valeroidine below).

The attempt at hydrogenolysis of scopolamine hydrobromide with $LiAlH_4$ resulted in the formation of only scopoline (IV) presumably because of the great nucleophilic character of the lithium aluminum scopine complex formed. Hydrogenolysis with Raney nickel catalyst followed by hydrolysis of the ester VI, however, gave racemic 3,6-dihydroxytropane (VII) and (-)-tropic acid (V)[5]. The racemic 3,6-dihydroxytropane (VII) was identical



with the racemate synthesized by the Robinson method from α-hydroxysuccinaldehyde, methylamine and acetonedicarboxylic acid[6]. The racemate VII (from scopolamine) was resolved by the use of dibenzoyl-(+)-tartaric acid, and the levorotatory



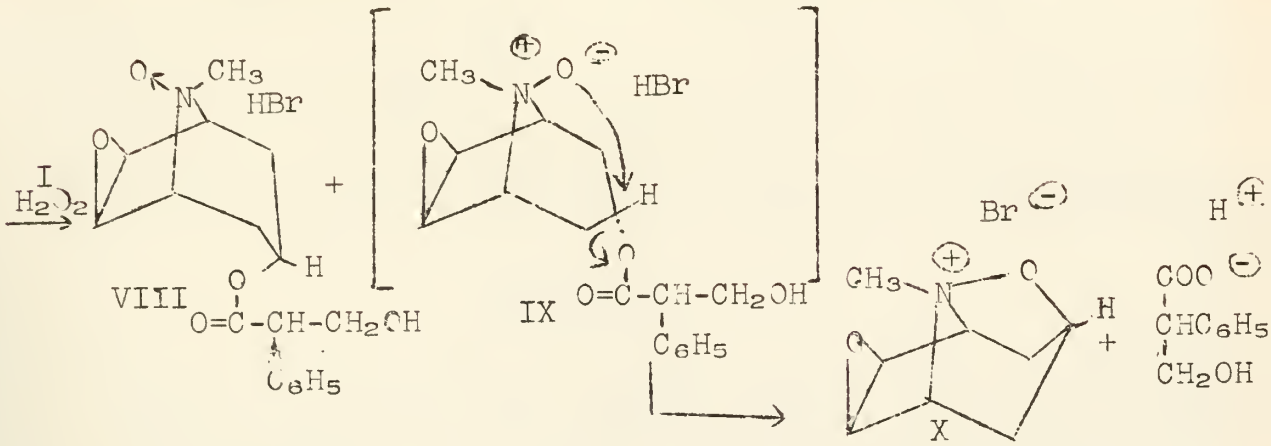
form proved to be identical with the (-)-3,6-dihydroxytropane obtained by hydrolysis of valeroidine (II)[8].

Since the C_6-hydroxyl group in norvaleroidine or (-)-6-hydroxynor-3-tropyl isovalerate (XIII) has been shown to have the β-configuration (see valeroidine below), the epoxide ring in scopolamine (I) must also have the β-configuration with respect to the nitrogen bridge. Thus the basic moiety of scopolamine (I) is shown to be 3α-hydroxy-6,7β-epoxytropane[5].

It is of interest to note that Meinwald[7] has arrived at the same conclusion on the configuration of scopolamine on the basis of the formation of scopoline (IV) and on the formation of scopolinium bromide (X) on oxidation of scopolamine hydrobromide with hydrogen peroxide, the formation of X being explained by

*The reference group is the $>N-CH_3$ bridge, and the substituent is β if it is on the same side as the reference group and α- if it is on the opposite side of the general plane of the seven-membered ring.

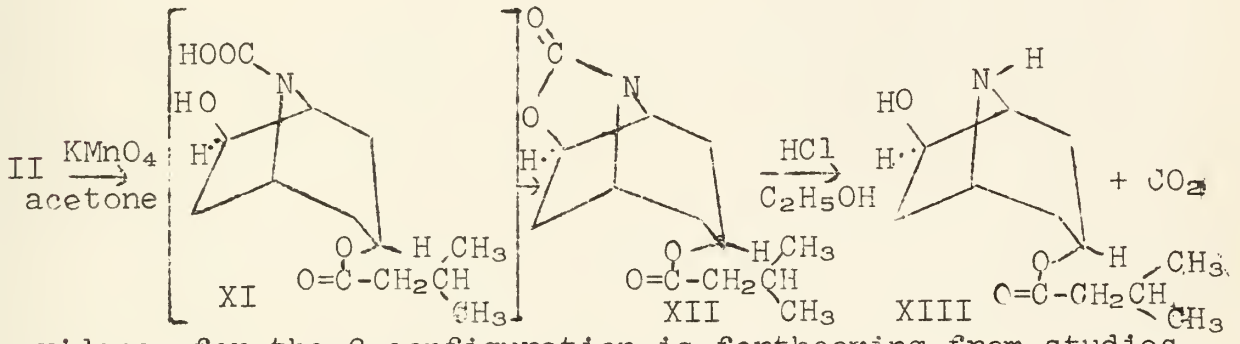
the internal displacement of the tropate ion from the epimeric



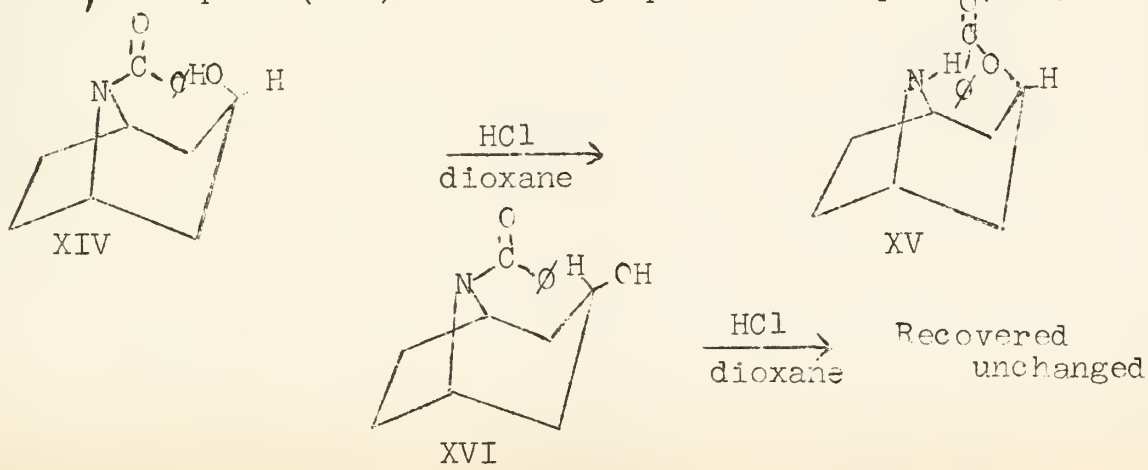
N-oxide (IX) which necessitates a trans relationship between the C_3-ester group and the nitrogen bridge. ψ-Scopine [C_3-epimer of scopine (III)] is stable under the same conditions. This is offered as further evidence for the α-configuration of the C_3 ester group of scopolamine (I).

Valeroidine:

The hydrolysis of valeroidine (II) has shown it to be a monoisovaleroyldihydroxytropane[8], and the basic moiety was shown to be identical with (-)-3,6-dihydroxytropane[5]. The C_6-hydroxyl of II was shown to have the β-configuration (cis to the nitrogen bridge) since the conversion of II to norvaleroidine (XIII) by oxidation followed by mild hydrolysis proceeded through a cyclic urethane intermediate (XII)[3]. Additional



evidence for the β-configuration is forthcoming from studies of the N→O acyl migration which has proved to be of value in determining the configuration of the hydroxyl group in nor-ψ-tropine (XIV) and its C_3-epimer nortropine (XVI)[10].



The C_3-ester group of valeroidine (II) was shown to have the α-configuration (trans to the nitrogen bridge) since the C_3-hydroxyl group of scopine (III) has the α-configuration (formation of a tetrahydrofuran derivative by backside attack on the epoxide bridge by treatment with alkali), and valeroidine can be converted by hydrolysis to the same (-)-3,6-dihydroxytropane as obtained from scopolamine (I) by hydrogenolysis followed by hydrolysis. Thus valeroidine appears to be the isovalerate of 3α,6β-dihydroxytropane[5].

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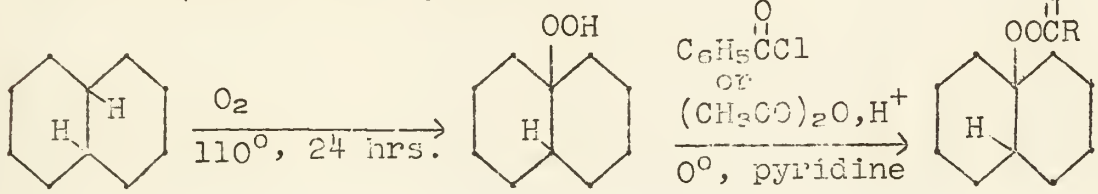
THE REARRANGEMENT OF TRANS-9-DECALYL PERESTERS

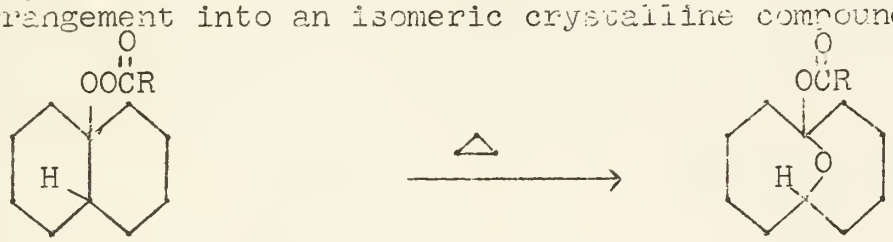
Reported by E. W. Flynn April 2, 1954

Criegee[1] in 1944 found that decalin (I) could be converted into a crystalline hydroperoxide (II), which under mild conditions is transformed into the acetate (III, R=CH_3) or benzoate (IV, R=C_6H_5) perester.



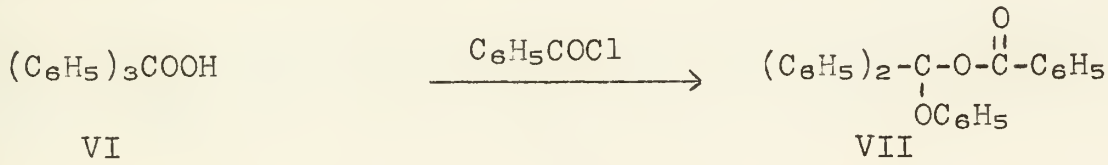
I II III or IV

He also observed that heating the perester alone or in an appropriate solvent, such as methanol, causes it to undergo rearrangement into an isomeric crystalline compound (V).



III or VI V

Criegee noted that this rearrangement was analagous to that encountered by Wieland and Maier[2] in the attempted benzoylation of tritylhydroperoxide (VI). Instead of the expected perbenzoate they obtained the isomeric compound (VII), in which the peroxidic oxygen atom interposed itself between two neighboring carbon atoms.



VI VII

Later, Criegee and Kaspar[3] investigated the mechanism of this rearrangement extensively. From their studies they concluded that formally the rearrangement of a decalyl perester is similar to the pinacol and Beckmann rearrangements, in which a migration occurs from one atom to a neighboring atom. They found that the ease of rearrangement of a decalyl perester depends upon the following three factors: (1) the strength of the acid used to form the perester, (2) the acidity of the hydroperoxide, (3) the solvent used to carry out the rearrangement.

Criegee and Kaspar found that the stronger the acid used to esterify the hydroperoxide, the greater the tendency for the rearrangement to occur. For example, the acetate and benzoate peresters of decalin can be caused to rearrange with a measurable velocity by warming, whereas the p-nitrobenzoate perester rearranges so readily that it can be isolated only

with difficulty. Warming in methanol at its boiling point causes the p-nitrobenzoate perester to rearrange completely within one minute. Under the mildest of conditions no perester of trichloracetic acid could be isolated but only its rearrangement product was obtained.

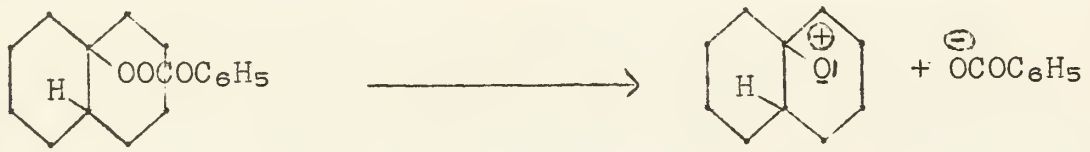
The acidity of the hydroperoxide was also found by Criegee and Kaspar to influence the rearrangement. As mentioned earlier Wieland and Maier[2] encountered a similar rearrangement in attempting to benzoylate tritylhydroperoxide. Criegee and Kaspar were able to prepare without difficulty not only the benzoate but also the p-nitrobenzoate perester of neopentyl hydroperoxide. Therefore, they concluded that the weaker the acid strength of the hydroperoxide the greater the tendency for the perester to rearrange, inasmuch as decalyl and trityl hydroperoxide do not possess sufficient acidity to form alkali salts.

Finally Criegee and Kaspar observed that the solvent in which the rearrangement is carried out has an important influence upon the rearrangement velocity. Some relative rates for the rearrangement of the perbenzoate ester in various solvents as determined by Criegee and Kaspar are as follows:

Solvent	Relative Rate
Acetic Acid	10^5
Methanol	2×10^4
Acetonitrile	200
Benzene	1

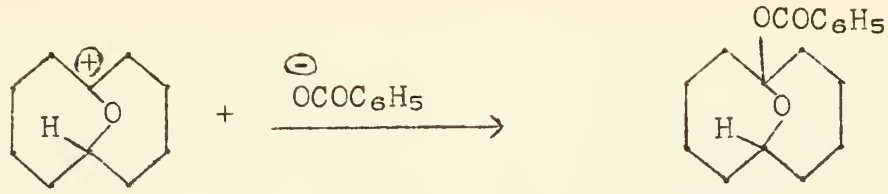
This increase in rearrangement velocity with increasing ionizing power of the solvent is analagous to the influence of the solvent in the Wagner-Meerwein[4] and Curtius[5] rearrangements.

Criegee suggested that the origin of the rearrangement lies in a strong polarization of the -O-O- bond in the perester which leads to the formation of a benzoate anion and a cation (VIII).



IV VIII

This cation, however, in which an oxygen atom possesses only an electron sextet is therefore unstable, and attempts to achieve stabilization by abstracting an electron pair from a neighboring carbon-carbon bond, resulting in the formation of the cation (IX) in which the positive charge resides on carbon. This cation (IX) then recombines with the benzoate anion to form the rearranged ester (X).



IX X

Criegee states however, that this mechanism does not mean to imply that the benzoate anion completely dissociates during the rearrangement but that he believes the rearrangement to occur in 'molecular association' of the ester.

This scheme proposed by Criegee for the rearrangement of a decalyl perester is patterened after the general mechanism formulated by Whitmore[3] for rearrangements involving 1,2-migrations, and apparently there is a number of analgous rearrangements involving carbon to oxygen migrations.[7,8,9,10]

Recently two groups of investigators, Bartlett and Kice[11] at Harvard and Goering and Olson[12] at the University of Wisconsin, obtained similar results in studying the mechanism of the rearrangement of decalyl peresters.

Bartlett and Kice[11] investigated the kinetics of the rearrangement of some benzoates of 9-decalyl hydroperoxide and found that the rearrangement was of the first order, showing only moderate acid catalysis. They also observed that the rates of rearrangement of the substituted benzoates bearing the nitro, bromo, methyl and methoxy substituents in the para position fit the Hammett equation with a value of $\rho = 1.34$, compared to 1.00 for the ionization of benzoic acids. This is in accord with the polarizability of the -O-O- bond and confirms the essential ionic nature of the rearrangement.

Goering and Olson[12] were particularly interested in determining to what extent, if any, dissociation into free ions might be occurring. In order to obtain information on this point they studied the rearrangement of decalyl peresters in the presence of foreign anions to see if the isomeric rearrangement would be diverted by interchange of anions.

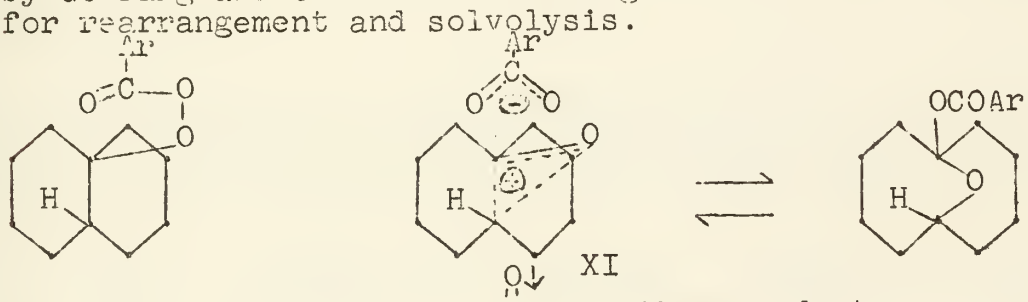
Decalyl perbenzoate was rearranged in methanol and aqueous methanol in the presence of lithium p-nitrobenzoate and decalyl p-nitroperbenzoate was rearranged in similar solvents in the presence of benzoate ions. The results obtained by Goering and Olson show that there was no detectable amount of anion interchange in the rearrangement of either the decalyl benzoate or p-nitrobenzoate perester. This fact was also demonstrated by Bartlett and Kice[11] who rearranged the benzoate perester in the presence of sodium p-bromobenzoate under similar conditions and found that the ester produced did not contain any appreciable amount of bromine.

In addition Goering and Olson found that the acid isolated from the rearrangement contained appreciable amounts of the acid from which the perester was formed, even though the analysis of the rearranged ester clearly showed that exchange had not occurred. The presence of this acid was found

to be the result of the simultaneous formation of rearranged ester and acid when the perester is rearranged in methanol or aqueous methanol. That the acid which accompanies the rearranged ester is formed during and not subsequent to the rearrangement was shown by the fact that neither the rearranged benzoate nor p-nitrobenzoate perester produces any measurable amount of acid under the conditions of the rearrangement. The ratio of rearrangement to solvolysis of decalyl perbenzoate in methanol was determined by Goering and Olson and found to be temperature dependent, decreasing with an increase in temperature.

The intramolecular nature of the rearrangement together with a simultaneous solvolytic reaction suggests that the rearrangement of decalyl peresters in methanol falls into the class designated 'internal rearrangements' by Winstein and co-workers[13]. There appears to be very close parallelism between the present case and certain allylic[14], homoallylic[13] and Wagner-Meerwein[5] rearrangements which similarly are internal and accompanied by solvolysis.

The rearrangement of decalyl peresters has been formulated by Goering and Olson as involving a common intermediate (XI) for rearrangement and solvolysis.



Ar = C_6H_5 or p-$NO_2C_6H_4$ HOCAr + other products

As far as the rearrangement is concerned the present formulation is similar to the one proposed by Criegee with the exception that it is now clear that the intermediate does not involve free ions to any extent and can probably best be described as an 'ion pair.'

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PREPARATION OF ALDEHYDES BY USE OF LITHIUM ALUMINUM HYDRIDE

Reported by Paul R. Jones April 2, 1954

Introduction and History

Soon after lithium aluminum hydride was made available on a commercial scale, it was used as a reducing agent in the preparation of alcohols, amines, and hydrocarbons. It was announced in 1948[1] that the reagent could be employed to convert nitriles and amides into aldehydes in preparative yields. Since that time lithium aluminum hydride has been utilized in several ways to prepare aldehydes. The difference in products obtained in these reductions is partially controllable by the amount of reducing agent taken and by the reaction temperature. In the presence of an excess of lithium aluminum hydride complete reduction occurs (e.g., amides and nitriles are converted to amines; esters are converted to alcohols). If, on the other hand, less than one mole of reducing agent is used and the reaction is carried out inversely at -15°C., or lower, only partial reduction generally is observed.

From Nitriles

The formation of aldehydes from nitriles is believed to involve hydrolysis of the partially reduced nitrile.[2] If the imino intermediate is further reduced before hydrolysis occurs, then the product should be an amine. Since reduction of a

$$\begin{array}{ccccc} R\text{-}C{\equiv}N & \xrightarrow{MH} & R\text{-}CH{=}NM & \xrightarrow{MH} & R\text{-}CH_2\text{-}NM_2 \\ & & \downarrow (H_2O) & & \downarrow (H_2O) \\ (M = \frac{LiAl}{4}) & & RCHO & & RCH_2NH_2 \end{array}$$

nitrile by this scheme would require only one hydride ion per molecule of nitrile, reduction should stop at the imino stage when 1/4 mole of lithium aluminum hydride is added inversely. Results corresponding to these conjectures have been obtained in several instances. Cyclopropylcyanide has been reduced in this manner to produce cyclopropylaldehyde in a 48% yield.[3] Certain dimethylaminoaldehydes have also been obtained in an analogous fashion:[4]

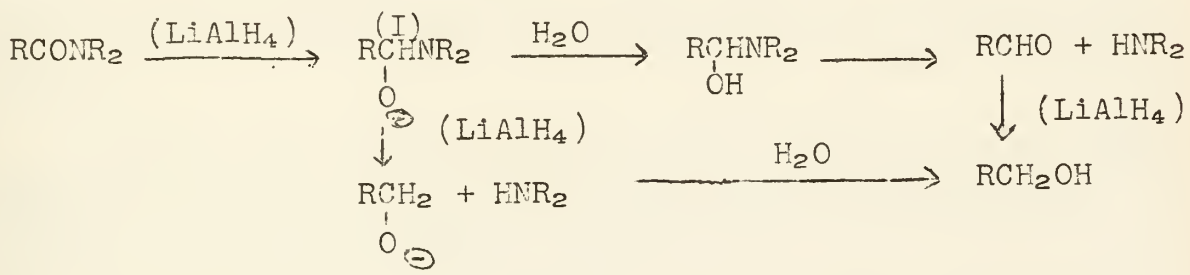
$$\begin{array}{c} CH_3CHCH_2CH(C_6H_5)CN \\ | \\ N(CH_3)_2 \end{array} \xrightarrow{1/4\ LiAlH_4} \begin{array}{c} CH_3CHCH_2CH(C_6H_5)CHO \\ | \\ N(CH_3)_2 \end{array}$$

Trifluoroacetaldehyde, whose synthesis by various reductions, hydrolyses, and oxidations had failed, was finally prepared in a 46% yield by reduction of the nitrile with 1/4 mole of lithium aluminum hydride.[5]

From Amides

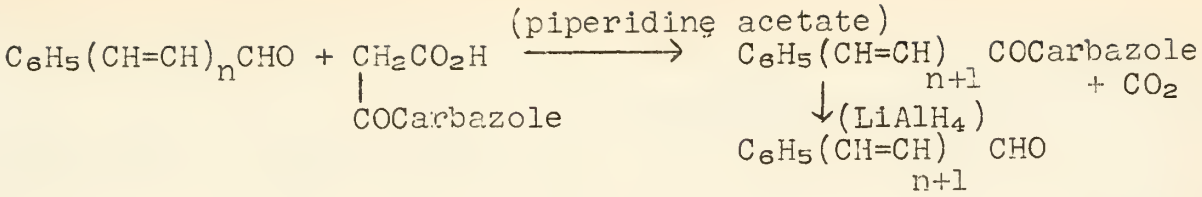
Amides, like nitriles, yield amines when treated with a sufficient quantity of lithium aluminum hydride; and, like nitriles, they can be made to produce aldehydes in some cases

when 1/4 mole of reducing agent is used. The circumstances under which amides and nitriles are converted to aldehydes are apparently not the same, however, because in addition to aldehydes, amides also produce considerable amounts of alcohols under certain conditions.[6] Since for the most part it is in the inverse reactions that alcohols have been detected, it is possible to visualize the alcohol as a further reduction product of the aldehyde. One group of workers[6] has suggested that subsequent reduction of the aldehyde complex or of the free aldehyde (formed by hydrolysis of the complex) may occur.



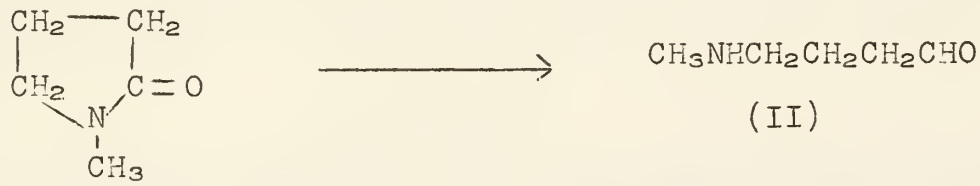
They concluded that (I) was stable toward further reduction because the addition of 0.5 mole of lithium aluminum hydride caused no change in the yield of the aldehyde. The alternative scheme of hydrolysis, followed by reduction of the aldehyde, may well represent the true course of the reaction. One of the problems of the above scheme is whether decomposition of the aldehyde intermediate does occur before the reaction mixture is worked up. If it does, presumably further reduction would be more rapid than the initial reduction step. These workers concluded, as did Weygand,[7] that the amount of aldehyde obtained increased with the steric hindrance about the nitrogen atom. Experimental results bear out this conclusion quite well. bis-(N,N-Dimethyl) phthalamide, which fails to react with methylmagnesium bromide, gave phthalaldehyde in a yield of about 70%.[7] Similar aldehyde preparations have been carried out on the N-methylanilides of acetic, succinic, malic, benzoic, salicylic, phthalic, and 2,4-dimethoxy-o-phthalic acids in yields ranging from 54% to 75%.[8] The bis-piperidide of phthalic acid also gave the aldehyde in satisfactory amounts. Contrary to Weygand, however, these workers observed that the production of the alcohol also increased with steric hindrance.

It is interesting to note that, when the nitrogen is part of an aromatic ring, successful syntheses of aldehydes have been consistently observed. Benzoylpyrrole,-indole, and -carbazole give yields of benzaldehyde ranging from 54-60%.[6] When cinnamamides are treated with lithium aluminum hydride in the normal fashion, no amine but a 29% yield of cinnamyl alcohol is obtained. It was therefore surprising to find that an inverse treatment of the carbazole amide resulted in a 45% yield of cinnamaldehyde. An inverse reaction on the ordinary cinnamamides gave no products at all. Advantage has been taken of this behavior of α,β-unsaturated carbazole amides to produce polyenes:[9]

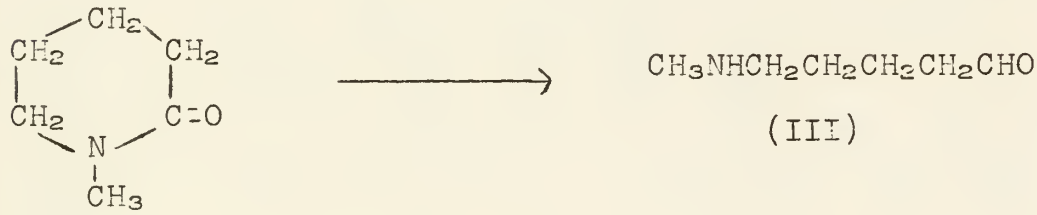


It has been thought that the carbonyl group in a pyrrole-type amide should be more like that of a ketone than that of an ordinary amide.[9] Consequently the condensation of N-acetylcarbazole with cinnamaldehyde in the presence of calcium ethoxide was attempted. Only a trace amount of the expected condensation product was found, but when the 3-nitrocarbazole was substituted for carbazole, 21% of the new amide was obtained.

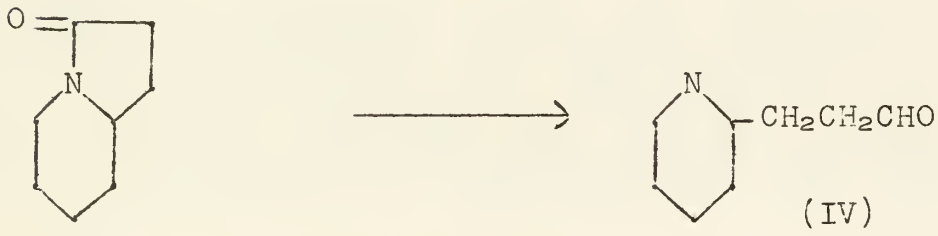
Lactams, being inner amides, might be made to give aldehydes on reduction. Certain γ- and δ-substituted amino aldehydes have been prepared from lactams in the inverse manner with lithium aluminum hydride:[10]



(II)



(III)

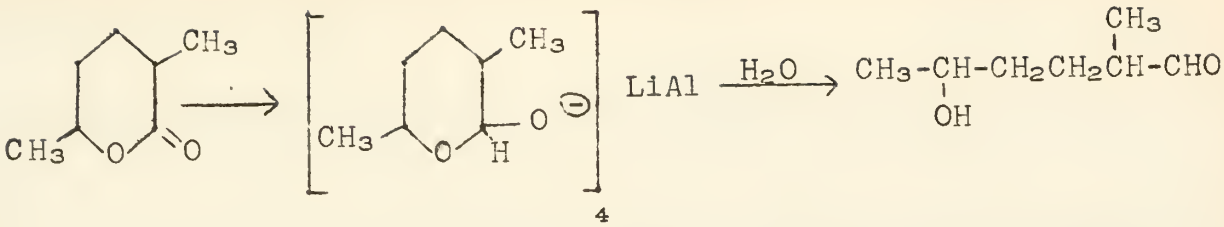


(IV)

The synthesis of (IV) is interesting because it has the structure which has been ascribed to pelletierine, an alkaloid obtained from the pomegranate tree. These workers[10] found that the synthetic compound did not show the properties of pelletierine. The reaction scheme for lactam reduction may be analogous to that already described for non-cyclic amides.

From Lactones

By virtue of the similarity in structures of lactams and lactones, it is not surprising that the latter, unlike esters, do produce aldehydes which are the expected γ- or δ-hydroxy aldehydes.[11] Again the proposed intermediate is like that of the amide and lactam. The preparation of 2-methyl-5-hydroxy-hexanal is illustrative:



Sodium borohydride has been used to convert lactones to aldehydes in the carbohydrate field because, unlike lithium aluminum hydride, it can be used in water solution.[12]

From Orthoesters

The preparation of aldehydes is possible from orthoesters because the acetal, which is the first reduction product, is stable toward further reduction and can be hydrolyzed by acid to the aldehyde.[13] The methyl acetal of β-methylmercaptopropionaldehyde was prepared in a 95% yield from the orthoester of β-methylmercaptopropionic acid. Other orthoesters that were successfully converted to their acetals and subsequently to the aldehydes were those of formic, acetic, and valeric acids.

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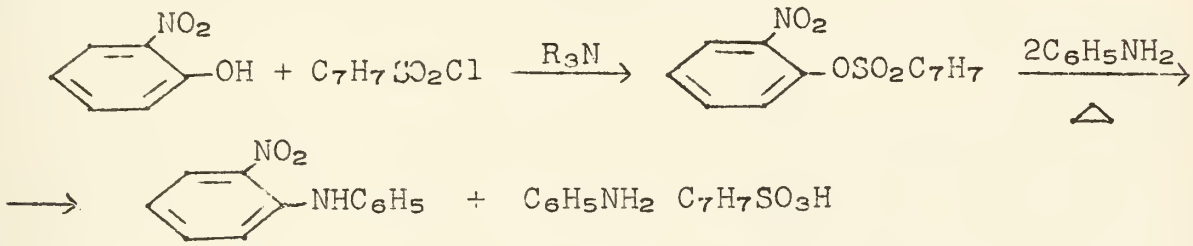
THE ULLMANN-NÁDAI REACTION

Reported by H. Ruus April 9, 1954

The replacement of the hydroxyl group by chlorine in polynitrophenols using p-toluene sulfonyl chloride is called the Ullmann-Nádai reaction.

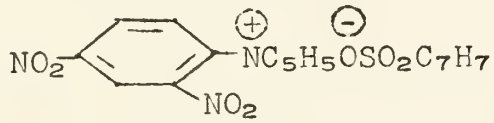
In 1908 Ullmann and Nádai prepared many o-nitroamines by treating the p-toluene sulfonate of o-nitrophenol and its derivatives with amines. The sulfonates were prepared by treating the phenols with tosyl chloride.



When the same procedure was applied to 2,4-dinitrophenol a mixture of 2,4-dinitrochlorobenzene and 2,4-dinitrophenyl p-toluene sulfonate was isolated. This method cannot be used for preparing amines of trinitrophenols. Picric acid gives only picryl chloride upon reaction with tosyl chloride in the presence of diethylaniline. Also, 2,4,6-trinitro-m-cresol gives only the chloro compound. Picric acid and tosyl chloride with pyridine did give picrylpyridinium p-toluene sulfonate[2] which in turn with hydrochloric acid gives picryl chloride. When pyridine is used as a base in the Ullmann-Nádai reaction usually ethersformation and quaternary pyridinium salts are formed in considerable amounts.[3]

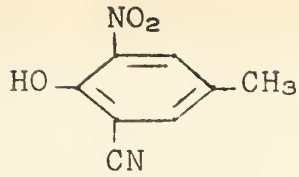
It has been observed that mononitrophenols do form p-toluene sulfonates with tosyl chloride in the presence of sodium carbonate and diethylaniline. Polynitrophenols in the presence of sodium carbonate yield esters but with diethylaniline are converted into polynitrochlorobenzenes.

2,4-Dinitronaphthol p-toluene sulfonate reacts with aniline to give the α-naphthylamino derivative. 2,4-Dinitrophenol with pyridine and tosyl chloride gives a pyridinium salt.



Since it is highly unlikely that the sulfonate group can dissociate as a negative ion Bell[2] explains these reactions by the combination of the amine and the nitro group in a way that the normal electron attracting character of the nitro group is lost. This is analogous to the Bennett and Willis[4] suggestion that bases can add to the nitro group.

The Ullmann-Nádai reaction has been tried with many compounds. It has been unsuccessful with the following compounds:



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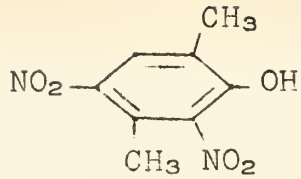

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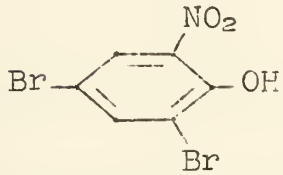

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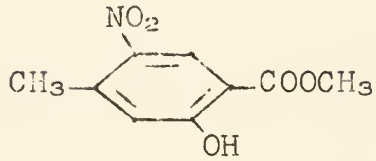
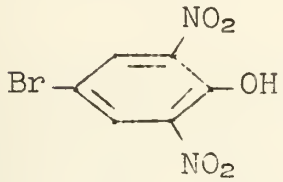


7

but has been successful with the following compounds:



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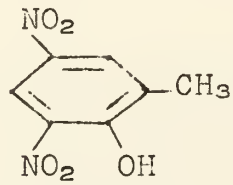

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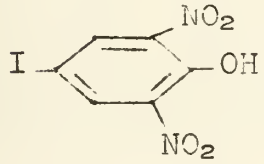

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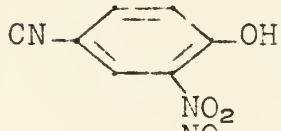
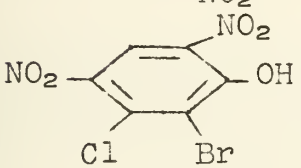


6
5% yield



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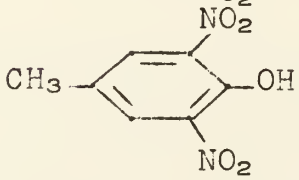
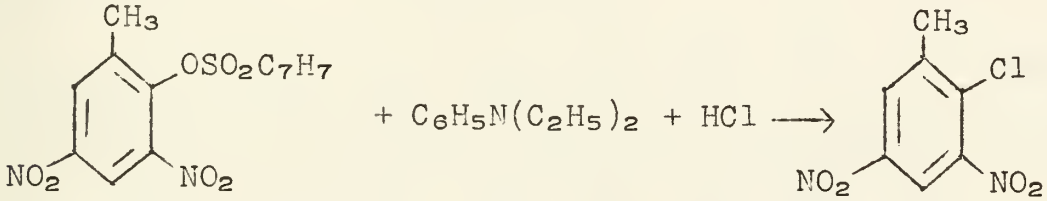


8

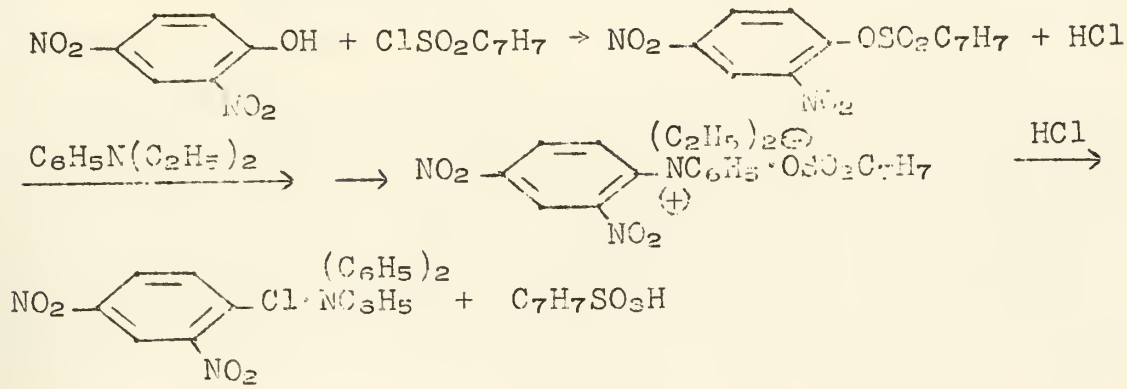
From this list one can see that two nitro groups must be on the ring in order that the replacement of hydroxyl by chlorine can occur. When electron donating groups are present on the ring the reaction does not occur or gives poor yields. An exception is the presence of one methyl group.

In 1927 Borsche and Feske[9] suggested a mechanism for the Ullmann-Nádai reaction. The authors assumed that because the p-toluene sulfonates are the normal reaction products of dinitrophenols with tosyl chloride, the dinitrochlorobenzenes are formed from the esters by the action of hydrogen chloride. To prove this they treated 3,5-dinitro-o-cresyl p-toluene sulfonate with 5N hydrochloric acid in the presence of diethylaniline.



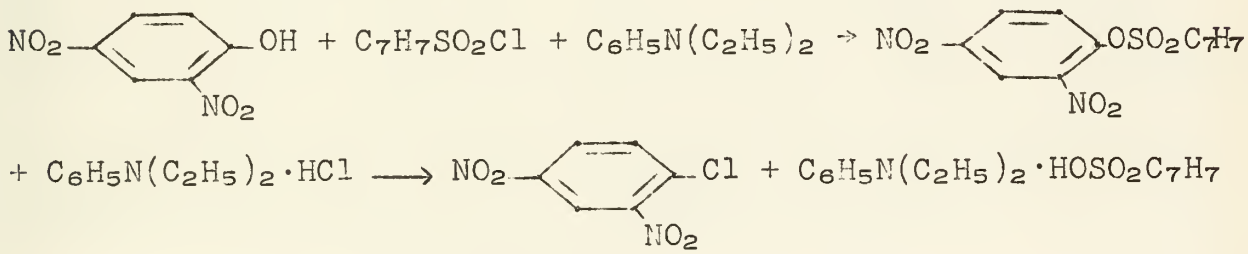
3,5-Dinitro-2-chlorotoluene was obtained in about the same yield as when prepared directly from 3,5-dinitro-o-cresol. In order to determine the role of the tertiary amine in the reaction they heated the 3,5-dinitro-o-cresyl sulfonate and the quaternary salt of the ester separately with pyridine and 5N hydrochloric acid. The first reaction gave only 3,5-dinitro-o-cresol. The second gave 3,5-dinitro-2-chlorotoluene in good

yield. Therefore they proposed the following sequence of reactions:



Klamann[10] studied the reaction of esters of 2,4-dinitrophenols with pyridine hydrochloride and found that the p-toluene sulfonate and acetate did give 2,4-dinitrochlorobenzene upon heating. If water was present hydrolysis took place. When aniline hydrochloride was used acetanilide and N-phenyl-2,4-dinitroaniline were obtained in addition to the chloro compound.[11] The esters of unsubstituted phenols under the same conditions did undergo the Fries rearrangement.

According to results of the experiments with tosyl esters of polynitrophenols Klamann believes that the formation of polynitrochlorobenzenes is a direct reaction between the polynitrophenyl ester and the hydrochloride of the tertiary base.[12] The quaternary pyridinium salt of 2,4-dinitrophenyl p-toluene sulfonate gives only an 18.8% yield of 2,4-dinitrochlorobenzene. When the ester is treated with pyridine hydrochloride the yield was 74.5%. He proposed the following sequence of reactions:



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AN INTERPRETATION OF META ORIENTATION IN THE ALKYLATION OF TOLUENE

Reported by Robert J. Harder April 9, 1954

In contrast to the relatively clear-cut ortho-para-orientation observed in the halogenation and sulfonation of the monoalkyl benzenes, the alkylation of these aromatics with aluminum chloride and alkyl halides frequently yields large amounts of the meta isomer. Price and Ciskowski[1] in 1938 proposed that this apparently anomalous orientation could be accounted for by "normal" alkylation to the 1,3,4-trialkyl derivative, followed by loss of the alkyl group in the 4-position.

This view was questioned by Francis[2], who maintained that the 3-alkyl group should be more labile than the 4-alkyl, since the former is more out of position with respect to the directive effect of the other two alkyl groups[3]. Further, it was shown by Norris and Rubinstein[4] that aluminum chloride isomerizes o- and p-xylene to the meta isomer under normal reaction conditions, and these authors suggested that isomerization is a satisfactory explanation for the formation of meta isomer in Friedel-Crafts reactions. McCaulay and Lien[5] have found that it is possible to form larger amounts of the meta isomer than would be predicted on the basis of the calculated equilibrium values, and they have postulated that this may be accounted for by assuming that the meta isomer forms more stable σ-complexes with the catalyst than the ortho and para isomers.

Brown and Nelson[6] have observed that the explanation given by McCaulay and Lien is sufficient to account for the high yields of meta isomer obtained under isomerizing conditions (in general, higher temperatures and large amounts of catalyst), but that it does not explain the formation of meta isomer under non-isomerizing conditions. Condon[7], for example, has shown that p-cymene is not isomerized to m-cymene under the same conditions that toluene is isopropylated to substantial amounts of m-cymene. In consequence, Brown and Nelson have introduced an interpretation of the formation of meta isomer in the alkylation of toluene under non-isomerizing conditions. This interpretation is based on the available literature concerning electrophilic substitutions of toluene in general.

Previous attempts[8-14] to account for the isomer distribution in aromatic substitution reactions have ignored the role of the attacking agent. Brown and Nelson have noted that there is no sharp division between reactions of toluene which yield little or no meta isomer and those which yield it in large amounts. This suggested that some property of the attacking agent may be important in determining orientation in these reactions. In Table I is listed a representative cross-section of some of these reactions.

TABLE I

Meta Substitution in Toluene

Reaction	Conditions	% Meta Isomer
Acetylation	$CH_3COCl + AlCl_3$	0
Bromination	Cl_2 in HOAc at 24°	0
Chlorination		0.5
Chloromethylation		Small
Nitration	$AcONO_2$ in Ac_2O at 0°	3.7
Sulfonation	100% H_2SO_4 at 35°	6.2
Methanesulfonylation	$MeSO_2Cl + AlCl_3$ at 100°	15
Mercuration	$Hg(OAc)_2$ at 110°	21
Isopropylation	$AlCl_3$-$MeNO_2$ at 65°	27.5

Brown and Nelson suggest that the amount of meta isomer formed in electrophilic substitutions of toluene is related to the "activity" of the attacking species, and they propose that this "activity" can be correlated with the electrophilic properties of these species. As a measure of this "activity" they utilize the relative reactivities of toluene and benzene toward the substitution reaction in question. For example, a highly active species such as the isopropyl carbonium ion is pictured as requiring less electron contribution from the aromatic ring in the transition state than a weakly active species such as bromine. Therefore, the contribution of electrons by hyperconjugative interaction in toluene will be less important with $(CH_3)_2CH^+$ than with Br_2. In consequence, $(CH_3)_2CH^+$ will attack either aromatic at about the same rate, whereas Br_2 will be highly selective between the two. Further, in toluene itself, the para- and meta-positions should be attacked at about the same rate by a species of low electron demand (i.e., highly active $(CH_3)_2CH^+$), while a species of low high electron demand (i.e., weakly active Br_2) should attack the para position greatly in preference to the meta position. Species of intermediate "activity" should give intermediate values for the para/meta ratios (P/M) and for the $k_{toluene}/k_{benzene}$ ratios (T/B).

In comparing the data in Table I with that in Table II, it is noted that insofar as the data overlap, the proportion of meta isomer increases with reactions having decreased selectivity between toluene and benzene.

TABLE II

Relative Rates of Substitution in Benzene and Toluene

Reaction	Conditions	$k_{toluene}/k_{benzene}$
Bromination	Br_2 in HOAc with I_2 at 25°	467
Chlorination	Cl_2 in HOAc at 24°	353
Nitration	$AcONO_2$ in Ac_2O at 0°	27
Acetylation	AcCl with $AlCl_3$ at 0°	13.3
Sulfonation	H_2SO_4 in $C_6H_5NO_2$ at 40°	8.4
Brosylation	p-$BrC_6H_5SO_2Cl$ with $AlCl_3$	5.1
Chloromethylation	CH_2O + HCl in HOAc at 85°	3.1
Isopropylation	C_3H_6 with $AlCl_3$ in CH_3NO_2 at 40°	2.1

Brown and Nelson have found that a plot of the log of the T/B reactivities versus the log of the P/M ratios for these reactions of toluene yields a simple linear relationship.

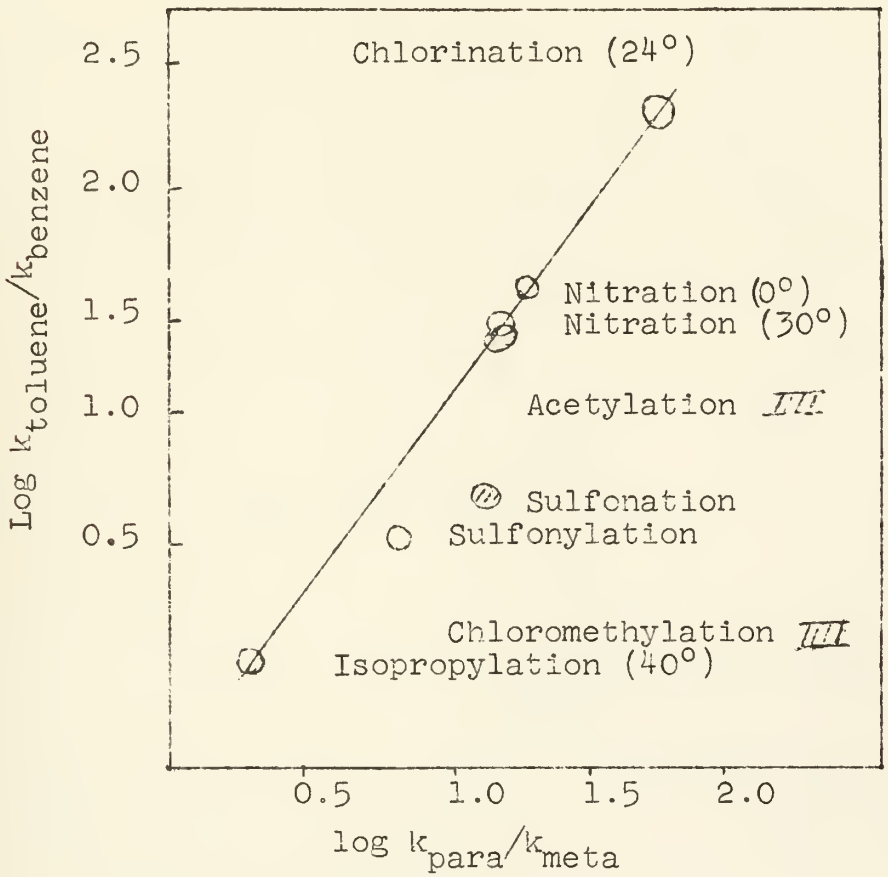

Fig. 1

There are, however, several serious discrepancies. For example, sulfonation yields too low a T/B ratio for the amount of meta isomer formed. However, these two values were obtained under widely different conditions. Acetylation also gives too low a T/B ratio, and this reaction is being investigated at the present time by Brown and H. L. Young. It is interesting to note that the discrepancy in the chloromethylation data led Brown and Nelson to reinvestigate this reaction, and as a result these authors found that the previously reported[15] T/B ratio was in error. Also, on the basis of their generalizations they predicted a T/B ratio of 15-20 for the mercuration of toluene, a value which was satisfactorily substantiated in their laboratory (found: T/B = 30±3).

It has been mentioned that the "activity" of the attacking species may be correlated with its electrophilic properties. Brown and Nelson point out that it would be reasonable to assign the following order of electrophilicity: $Br_2 < NO_2^+ < (CH_3)_2CH^+$. This is the order of "activity" observed in this treatment. They also predict that the electrophilic character of the following ions will increase in the order: $(CH_3)_3C^+ < (CH_3)_2CH^+ < CH_3CH_2^+$. That the t-butyl carbonium ion is less "active" than the isopropyl carbonium ion is borne out in the work by Schlatter and Clark[16], who report that the t-butylation of toluene yields only 7% of the meta isomer.

It should be noted that Brown and Nelson have compared the relative reactivity at the meta-position of toluene with that at the para-position, rather than that at the ortho-position where steric effects may be expected to operate. They point out that steric requirements may also influence the T/B reactivities while not affecting the P/M ratios. If, however, the partial rate factors for the para-position of toluene are used instead of the T/B ratios, then this effect should be minimized. As a result, these authors have plotted the log of the partial rate factors for the para-position (log p_f) versus the log of the ratio of the partial rate factors for the para- and meta-positions (log $(p/m)_f$). Again, a simple linear relationship exists between these terms, as shown in Fig. 2.

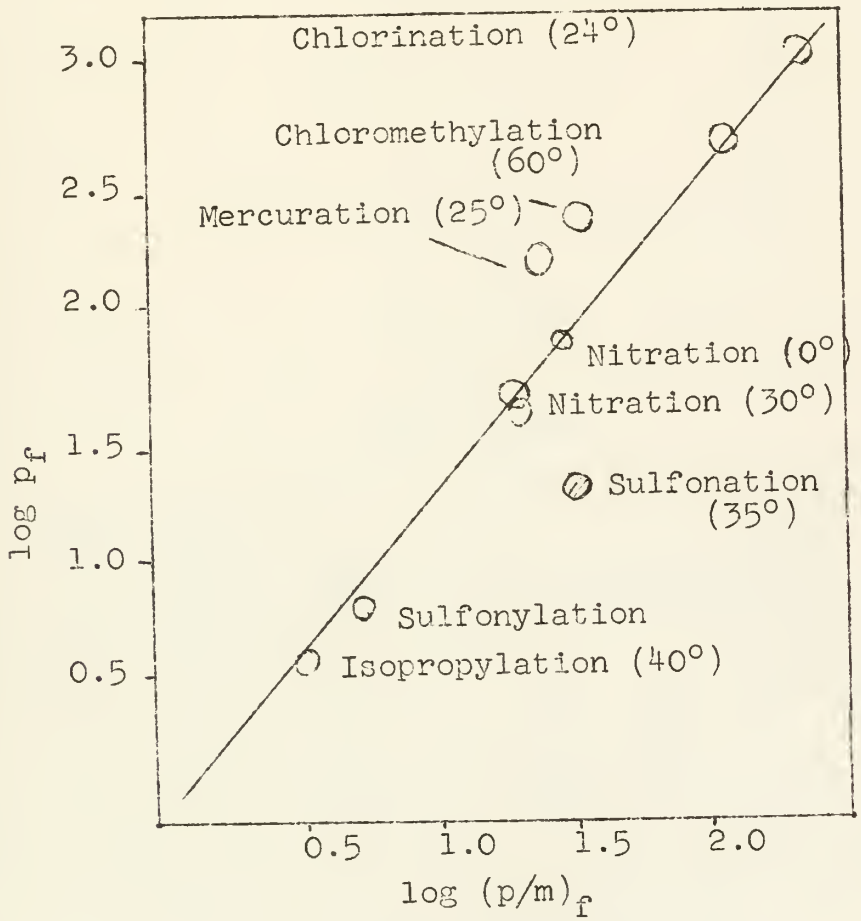

Fig. 2

Brown and Nelson propose that their treatment should be applicable not only to reactions of toluene but to electrophilic substitution of other monosubstituted aromatics as well. In the case of nitrobenzene, log p_f and log $(p/m)_f$ will have negative values. With aromatics having a halogen substituent, log $(p/m)_f$ should always have positive values, since these substituents are strongly ortho-para-directing. However, log p_f will have positive values only with attacking species of high "activity" and negative values with species of low "activity". Fig. 3 illustrates the predicted curves for nitrobenzene and chlorobenzene. Further study is needed to substantiate these predictions.

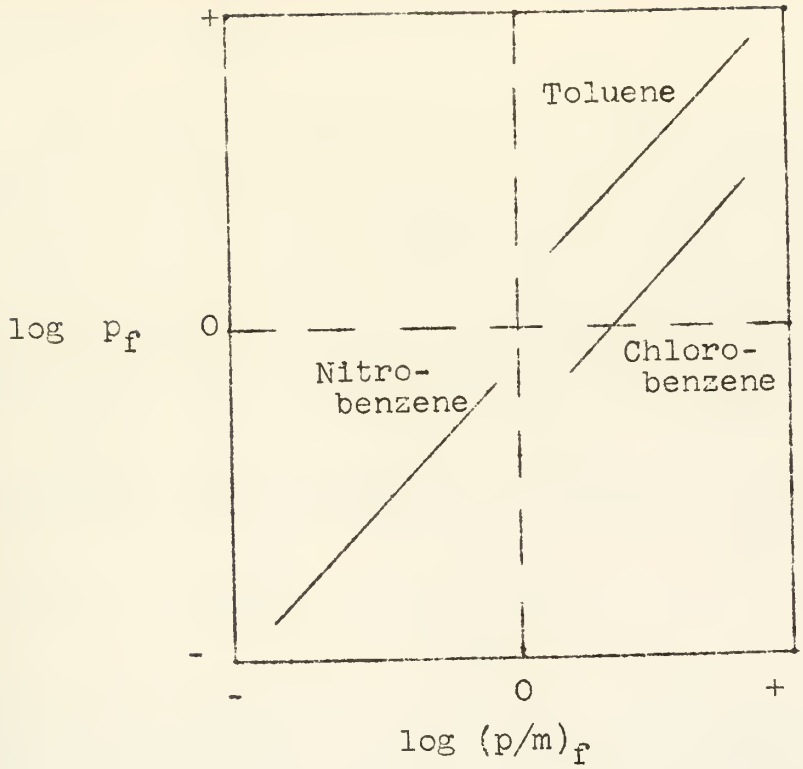

Fig. 3

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TELOMERIZATION

Reported by Edwin L. DeYoung April 23, 1954

The term telomerization was first used by Harman[1] and co-workers, although reactions of this type have been known since 1948[2]. Telomerization is a type of polymerization which may be either acid or free radical catalyzed. The process by which the end groups are formed is called chain transfer. A reaction of this kind, in which short chain compounds are formed, and the end groups are therefore chemically significant, is called telomerization, and the product is a telomer. The molecule which gives rise to the end group is called a telogen.

Joyce and co-workers[2], working with CCl_4 and ethylene obtained the following kinds of products. The structure of the

$$CCl_4 + n\,CH_2{=}CH_2 \xrightarrow[\substack{1500\text{ psi}\\ BZO_2}]{85^\circ C} Cl(CH_2\text{-}CH_2)_nCCl_3 \qquad n=1\text{-}4$$

telomer was proven by hydrolysis and characterization of the resulting ω-chloro acid. They discovered that the allowable ranges of benzoyl peroxide sufficient to catalyze the reaction were .003 - .0007 molequalar equivalents. They proposed the following mechanism for the reaction:

$$\text{Initiator } (BZO_2) \longrightarrow R\cdot$$

$$R\cdot + CCl_4 \longrightarrow R\text{-}Cl + \cdot CCl_3$$

$$\cdot CCl_3 + CH_2{=}CH_2 \longrightarrow Cl_3CCH_2CH_2\cdot$$

$$Cl_3CCH_2CH_2\cdot + nCH_2{=}CH_2 \longrightarrow Cl_3C(CH_2CH_2)_{n+1}\cdot$$

$$Cl_3C(CH_2CH_2)_{n+1}\cdot + CCl_4 \longrightarrow Cl_3C\text{-}(CH_2CH_2)_{n+1}\text{-}Cl + \cdot CCl_3$$

Harmon and co-workers[1] extended the method using ethylene and $CHCl_3$, CH_2ClI, CH_2Cl_2, CH_2I_2, CH_2Br_2 and CH_3I. They noted that the chain length, n, varied inversely with the reactivity of the halomethane. The catalyst was benzoyl peroxide. Reactions were as follows:

$$CHCl_3 + nCH_2{=}CH_2 \xrightarrow[100^\circ C]{100\text{ atm.}} H\text{-}(CH_2\text{-}CH_2)_n\text{-}CCl_3 \qquad n=1\text{-}6$$

$$CH_2ClI + nCH_2{=}CH_2 \xrightarrow[95^\circ C]{500\text{-}600\text{ atm.}} I\text{-}(CH_2CH_2)_n\text{-}CH_2\text{-}Cl \qquad n=1\text{-}4$$

$$CH_2Br_2 + nCH_2{=}CH_2 \xrightarrow[100^\circ C]{310\text{-}350\text{ atm.}} Br\text{-}(CH_2CH_2)_n\text{-}CH_2Br \qquad n=1\text{-}4$$

$$CH_2Cl_2 + nCH_2{=}CH_2 \xrightarrow[200^\circ C]{75\text{-}100\ atm.} Cl\text{-}(CH_2CH_2)_nCH_2\text{-}Cl \quad n=1$$

$$CH_2I_2 + nCH_2{=}CH_2 \xrightarrow[95^\circ C]{425\text{-}450\ atm.} I\text{-}(CH_2CH_2)_n\text{-}CH_2I \quad n=1$$

$$CH_3I + nCH_2{=}CH_2 \xrightarrow[95^\circ C]{775\text{-}900\ atm.} I\text{-}(CH_2CH_2)_n\text{-}CH_2 \quad n=1$$

More recently, Ford and co-workers[3] have investigated the telomerization of ethylene with HCl. The reaction with styrene they obtained a product which had an average of 6.7

$$nCH_2{=}CH_2 + HCl \xrightarrow[100^\circ C,\ BZO_2]{100\text{-}1000\ atm.} CH_3\text{-}(CH_2\text{-}CH_2)_{n-1}\text{-}CH_2\text{-}Cl \quad n=1\text{-}9$$

styrene units per molecule. The reaction with allyl chloride yielded two products. (I) is evidently formed by simple addition of HCl, while (II) would be formed by peroxide addition of

$$CH_2{=}CH\text{-}CH_2\text{-}Cl + HCl \xrightarrow[100^\circ C]{BZO_2} \underset{(I)}{CH_3\text{-}\underset{Cl}{CH}\text{-}CH_2Cl} + \underset{(II)}{Cl\text{-}CH_2\text{-}\overset{CH_2\text{-}Cl}{CH}\text{-}CH_2CH_2CH_2}$$

HCl to 1 molecule of allyl chloride, followed by addition of the resulting molecule of 1,3-dichloropropane to another molecule of allyl chloride. They proposed the same type of reaction mechanism as Joyce.[2]

The ionic telomerization reactions have been less extensively investigated. The first work on this type of reaction was done by Jenner and Schrieber[4] in 1951. They determined that it was an acid catalyzed reaction midway between an addition reaction and vinyl polymerization. They used H_2SO_4 and $HClO_4$ as catalysts. The structure proof consisted of hydrolysis and characterization of the resulting unsaturated alcohol.

$$nCH_2{=}CH\text{-}CH{=}CH_2 + R\text{-}CO_2H \xrightarrow{HClO_2} H(CH_2\text{-}CH{=}CH\text{-}CH_2)_n\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}R \quad n=1\text{-}3$$

$R = CH_3$, C_2H_5

They postulated the following mechanism:

$$CH_2{=}CH\text{-}CH{=}CH_2 \xrightarrow{H^\oplus} \underset{(I)}{CH_3\text{-}CH{=}CH\text{-}CH_2^\oplus} \longleftrightarrow \underset{(II)}{CH_3\text{-}\overset{\oplus}{C}H\text{-}CH{=}CH_2}$$

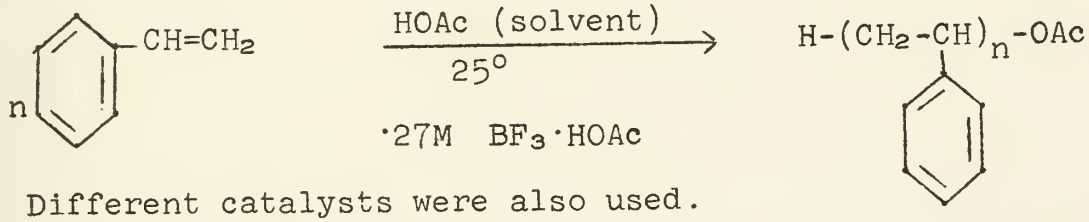
$$CH_2{=}CH\text{-}CH\text{-}CH_2$$

$$CH_3CH{=}CH\text{-}CH_2CH_2CH{=}CHCH_2^\oplus \xrightarrow{OAc^\ominus} CH_3CH{=}CH\text{-}CH_2CH_2CH{=}CH\text{-}CH_2\text{-}OAc$$

If structure (II) existed, some of the secondary alcohol should have been isolated. However, none of this was found.

With acetic acid as telogen, run in acetic anhydride as solvent at 25°C, the results were: n=1 (15%), n=2 (35%), n-3 (20%), n>3 (30%). With propionic acid as telogen run at -18°C, telomers of n=1-3 were isolated. With isoprene in aceti anhydride as solvent at 25°, n=12 for the telomer, and the yield using $HClO_4$ as catalyst was 49 times that using H_2SO_4 as catalyst.

The most recent work on ionic catalyzed telomerization has been done by Jenner and Coffman.[5] They studied the ionic telomerization of styrene using acetic acid, acetonitrile, and formaldehyde as telogens. The reaction with acetic acid was as follows:



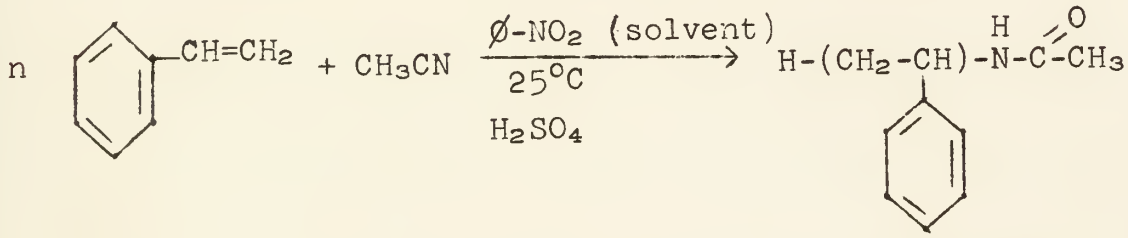
Different catalysts were also used.

·1M $HClO_4$ gave n=2 (25%)

·3M H_2SO_4 gave n=2 (28%)

n=1 (11%)
n=2 (38%)
n=3 (20%)
n>3 (31%)

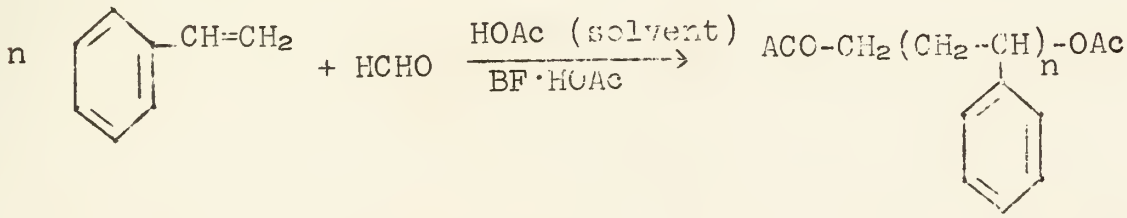
With acetonitrile, the reactions was as follows:



n=1 (21%)
n=2 (18%)

The ratio of styrene: CH_3CN:H_2SO_4 was 1:2:1

With formaldehyde the reaction yielded a diacetyl derivative.



n=1 (35%)
n=2 (17%)
n>2 (48%)

This reaction is somewhat similar to the well known Prins reaction.[6]

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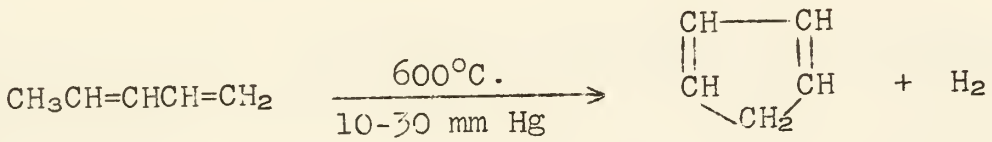
RECENT DEHYDROCYCLIZATION REACTIONS

Reported by William D. Smart April 23, 1954

Except for one instance, the conversion of pentadiene to cyclopentadiene[1], the only monocyclic carbon ring system that has been formed by dehydrocyclization is that of benzene.

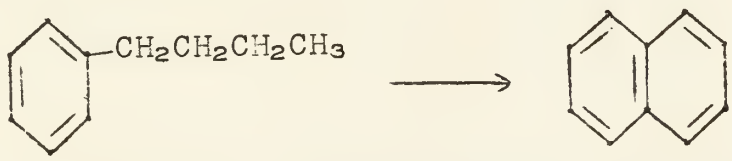


The formation of cyclopentadiene from 1,3-pentadiene, shown above, is interesting in that the reaction does not seem to be aided by catalysts. Kennedy and Hetzel found that by carrying out the reaction under reduced pressure good conversions to cyclopentadiene were obtained. They showed that the reaction was independent of catalysts and pressure, and suggested dehydrogenation by a free-radical mechanism.

Aliphatic alcohols have been successfully dehydrocyclized to aromatic compounds. Riesz and Thodos[2] working with a chromia-alumina catalyst at 450-475°C., showed that 1-hexanol was converted to benzene, 1-heptanol to toluene, and 1-octanol to a mixture of ethylbenzene, toluene, and xylenes. Repeating this work with pure chromia catalyst instead of the alumina-supported material, the reaction was found to take a different course[3], ketones being the final products. A four-step mechanism was suggested:

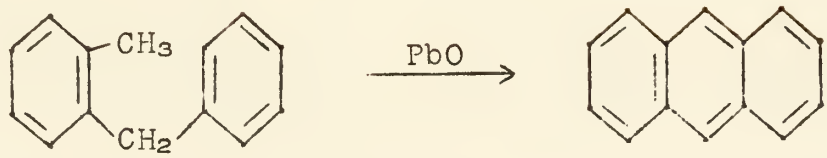
1. Dehydrogenation of alcohol to aldehyde.
2. Aldol condensation.
3. Loss of carbon monoxide from aldol to give a secondary alcohol.
4. Dehydrogenation of the secondary alcohol to give a ketone.

The examples of formation of polynuclear aromatic systems[4] by dehydrocyclication are so numerous that only a few typical reactions of different types will be mentioned. Included will be both recently reported and long known reactions, but pyrolysis of hydrocarbon mixtures will be omitted. Ferko[5] in 1887 found that ethylbenzene yielded naphthalene along with styrene, biphenyl, anthracene, phenanthrene, toluene, and benzene. More recent work with chromia catalysts at about 500°C. has shown that butylbenzene may be dehydrocyclized to naphthalene in yields as high as 50 per cent per pass[6].

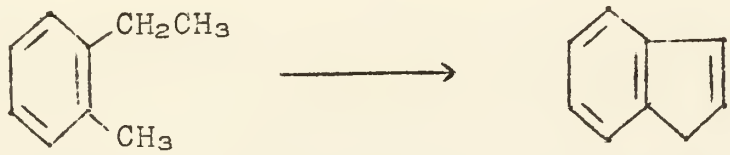


Anthracene has been obtained by the pyrolysis of toluene, ethylbenzene, or a mixture of benzene and styrene. Good conversions to anthracene were obtained by the dehydrocyclization

of o-benzyltoluene with lead oxide.

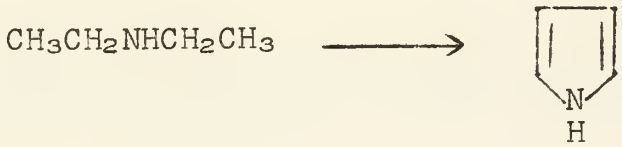


Indene has been made by the dehydrocyclization of o-ethyltoluene. The reaction was carried out by means of a chromia catalyst at temperatures of 540-620°C. or with an iron oxide catalyst at 650-700°C.

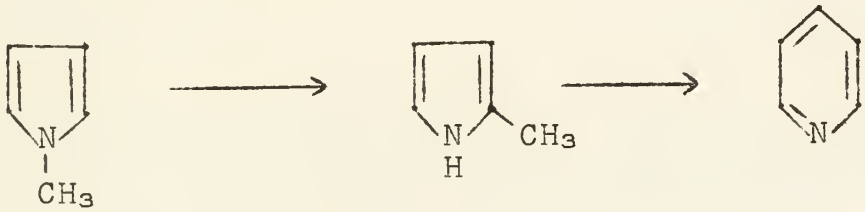


With ethylxylenes the products were methylindenes. n-Propylbenzene also undergoes dehydrocyclization to give indene.

Pyrrole has been reported to be formed from the pyrolytic dehydrogenation of diethylamine.



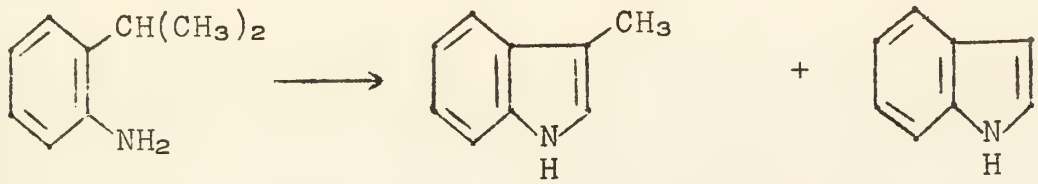
Pyridine has been made by a number of rearrangement-dehydrocyclizations. The pyrolysis of N-methylpyrrole gives pyridine by way of 2-methylpyrrole.



It has long been known that small amounts of indole could be formed by passing N-ethylaniline through a hot tube.

Later it was found that N,N-dimethyl-o-toluidine was converted by pyrolysis into N-methylindole, while N-methyl-o-toluidine at 330°C. with a nickel catalyst formed indole. More recently the catalytic conversion of o-ethylaniline to indole

has been investigated. With a chromium oxide-copper on carbon catalyst, 32 per cent conversion of o-ethylaniline to indole was obtained at 670°C. The attempt to extend this reaction to other o-alkylanilines was not very successful, the high temperatures necessary for reaction causing the starting material and the products to crack. Thus, o-isopropylaniline gave more indole than skatole[7].



The oxygen heterocycles synthesized by dehydrocyclization are limited presently to benzofuran and dibenzofuran and their simple derivatives. Benzofuran can be formed by the catalytic dehydrocyclization of o-ethylphenol at about 600°C., using either palladium or chromium oxide-copper on carbon catalysts. Conversions of 10-14 per cent benzofuran were obtained.

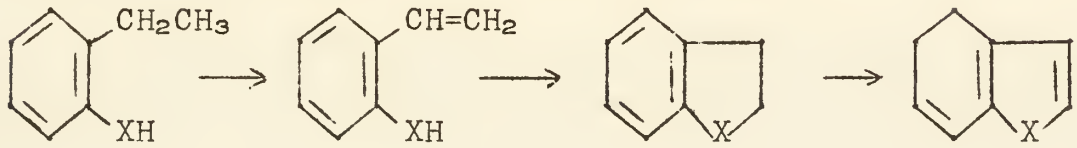
Pyrolysis of diphenyl ether yields dibenzofuran. Very little hydrogen is evolved in this reaction because it is consumed in the hydrogenolysis of the diphenyl ether to phenol and benzene.

The details of the mechanism of the catalytic dehydrocyclization reaction are still not completely understood. Investigation of the mechanism has been limited almost entirely to the conversion of simple paraffins and olefins into benzene and its alkyl derivatives.

It is believed that the first step in the reaction is the conversion of the aliphatic hydrocarbon into an olefin[8]. The next step is probably the conversion of the olefin to a naphthene which may or may not exist in the free state, i.e., the naphthene which is formed on the surface of the catalyst may never escape from the surface but be dehydrogenated to the aromatic, which then leaves the catalyst surface.

It has been observed in cyclizing various branched and straight chain paraffins over a platinum-carbon catalyst at about 310°C. that the greater the branching of the chains and the higher the molecular weight the greater the amount of aromatic compounds formed.

The following mechanism[7] has been suggested for the dehydrocyclic formation of the heterocycles,



where X may be S, O, or NH. The relative order of ease of cyclization of the three compounds is SH > OH > NH_2. This is the same order in which these groups tend to dissociate a proton, and it may be that the cyclization of these compounds occurs by addition of the ortho functional group across the ethylene side chain.

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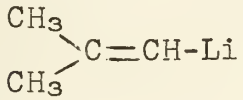
ALKENYLATION EMPLOYING LITHIUM ALKENYLS

Reported by Joseph E. Dunbar April 30, 1954

Introduction---Alkenylation cannot generally be accomplished by the use of Grignard reagents, since alkenyl halides with the halogen atom adjacent to the ethylenic bond do not form alkenylmagnesium halides except in the case of some arylvinyl bromides[1]. Vinyl bromide yields only acetylene[2] upon treatment with magnesium. This limitation has been overcome to some extent by alkynylation followed by semihydrogenation[3], but this is not always easily achieved, especially in the presence of various functional groups.

During the past four years Braude and coworkers have been developing a general method for the alkenylation of carbonyl compounds with lithium alkenyls. Some alkenyl-lithium reagents which have been used synthetically are isobutenyl-[4,5], cyclohexenyl-[4,6], propenyl-[4,7], 6,6-dimethylcyclohexenyl-[8], 5,5-dimethyl-3-methylidenecyclohexenyl-[9], cycloheptenyl-[10], and 4-methyl-1,3-pentadien-2-yl-lithium[9].



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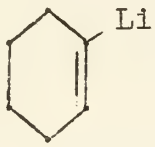

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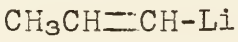

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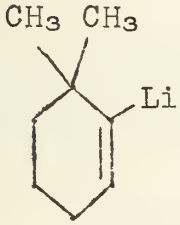

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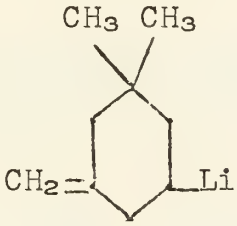

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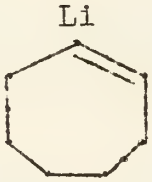

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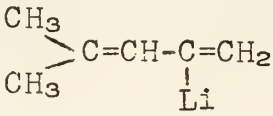


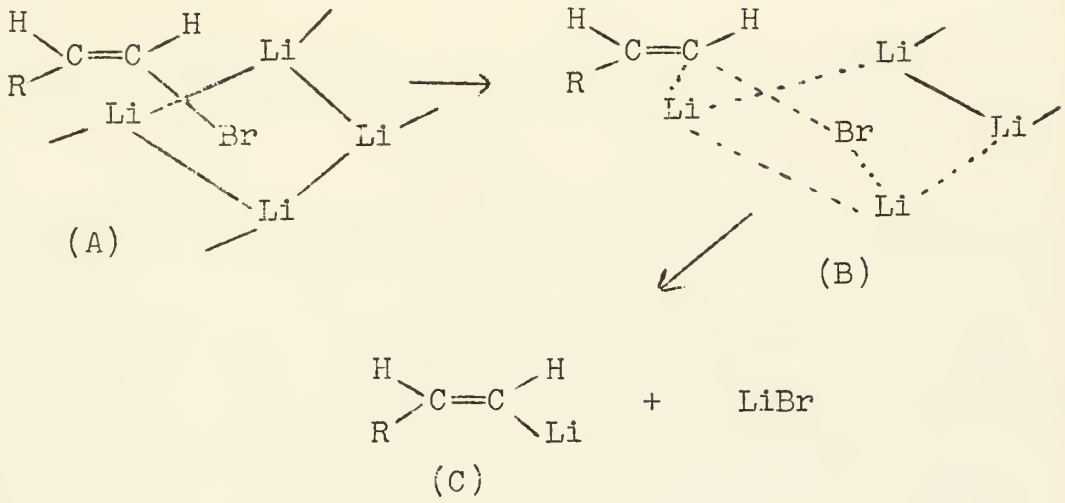
(VII)

Formation of Lithium Alkenyls --- Lithium alkenyls are prepared by the action of lithium on alkenyl bromides or chlorides in inert solvents such as ethyl ether or petroleum ether. The reagents are not isolated but are used in the solutions in which they are prepared.

Braude and Coles[7] have shown that formation of lithium derivatives is not limited to β,β-disubstituted and cyclic alkenyl halides by the metallation of propenyl bromide to give propenyl- and propynyl-lithium in a 5:1 ratio and in a total yield of 50%.

Reactions of lithium derivatives of cis-propenyl bromide with ketones or aldehydes result in the formation of cis-propenylcarbinols exclusively[7]. It is suggested that the metallation takes place on the surface of the lithium-metal

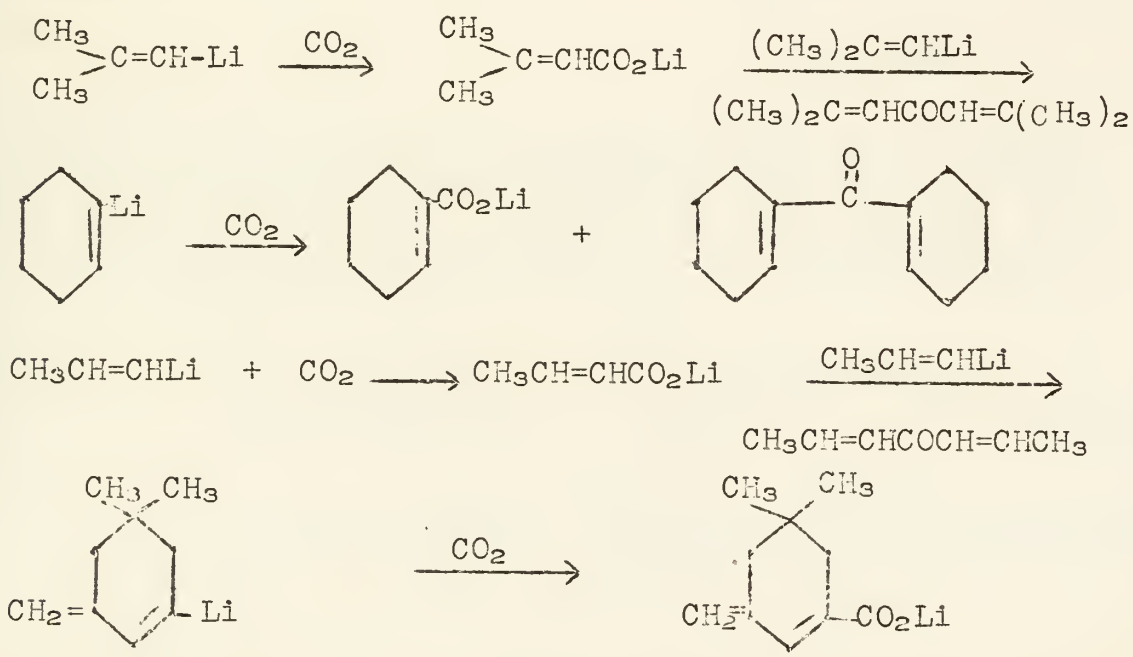
crystal in the following manner:



The distance between neighboring atoms in the lithium crystal is ca 3 Å, and the length of the carbon-bromine bond is ca 1.5 Å; but in view of the large size and polarizability of the halogen atom, the planar transition state (B) is, according to Braude, feasible and accounts for retention of geometrical configuration.

Only in the case of isobutenyl bromide[5] has a Wurtz-type coupling reaction been observed to accompany metallation with lithium.

Reactions of Lithium Alkenyls --- Carboxylation of lithium alkenyls affords the expected lithium salts of the α,β, unsaturated carboxylic acids as well as dialkenyl ketones [4,5,6,7,9].



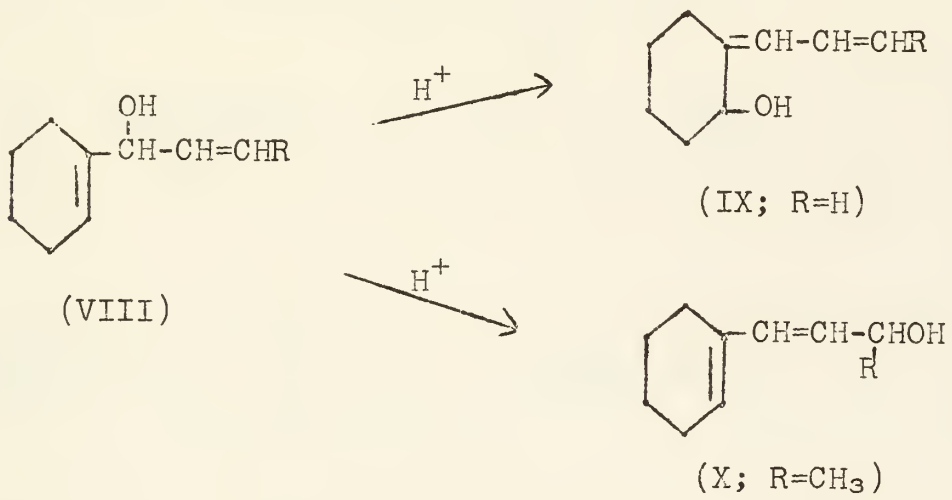
In the latter case[9] no dialkenyl ketone was isolated. The yield of carboxylic acid can be increased at the expense of the ketone when the carboxylation is carried out with a large excess of Dry Ice.

Lithium alkenyls react with lithium salts of carboxylic acids to give alkenyl ketones in 30 to 40% yields[11].

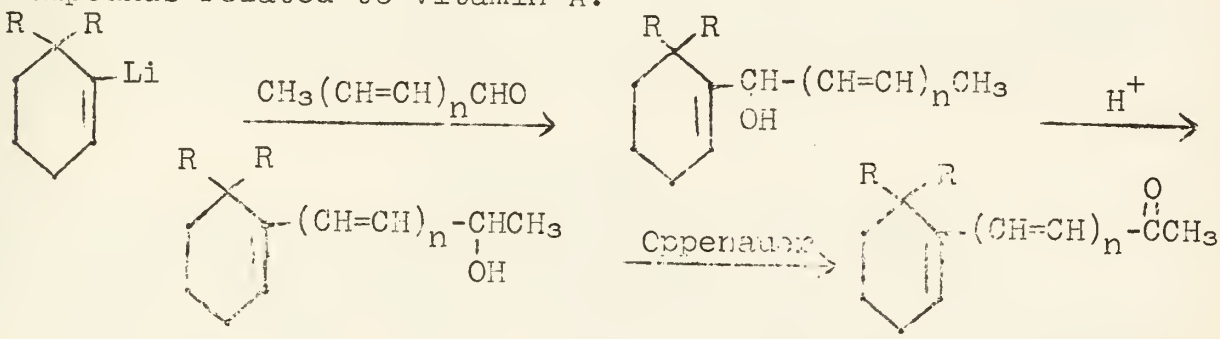
$$R_2C{=}CHLi \xrightarrow{RCO_2Li} R_2C{=}CHCOR$$

Treatment of lithium alkenyls with acyl chlorides results in the formation of the desired ketones only in very small yields.

Lithium alkenyls react with carbonyl compounds in the normal fashion to give the carbinols in yields of 40 to 60%. This procedure has been used to prepare a variety of unsaturated carbinols and polyenes[5,6,8,12,13,14,16]. Condensation of cyclohexenyl-lithium with acrolein or crotonaldehyde gave the expected carbinols (VIII; R=H or CH_3) in 45% and 60% yields, respectively[6].



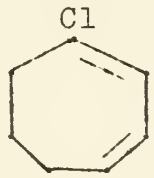
On treatment with dilute acids (VIII) isomerizes to (IX) or (X) with the hydroxyl group migrating toward the γ-carbon atom possessing the greater electrophilicity. Braude, Bruun, Weedon and Woods[8,14] have used this general procedure to furnish polyene ketones for possible use in the synthesis of compounds related to vitamin A.



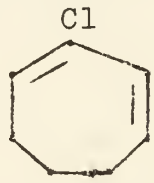
(R=H or CH_3)

Lithium alkenyls undergo the expected 1,2- and not 1,4-addition with ethylenic ketones[13], although 1,4-additions of lithium derivatives to ethylenic ketones have been reported[15].

Recently[9] several lithium alkadienyls have been made. Results of preliminary studies of reactions of the acyclic lithium alkadienyls, however, indicate limited synthetic usefulness because of side reactions which take place. A chlorocycloheptadiene (either structure XI or XII) proved un-



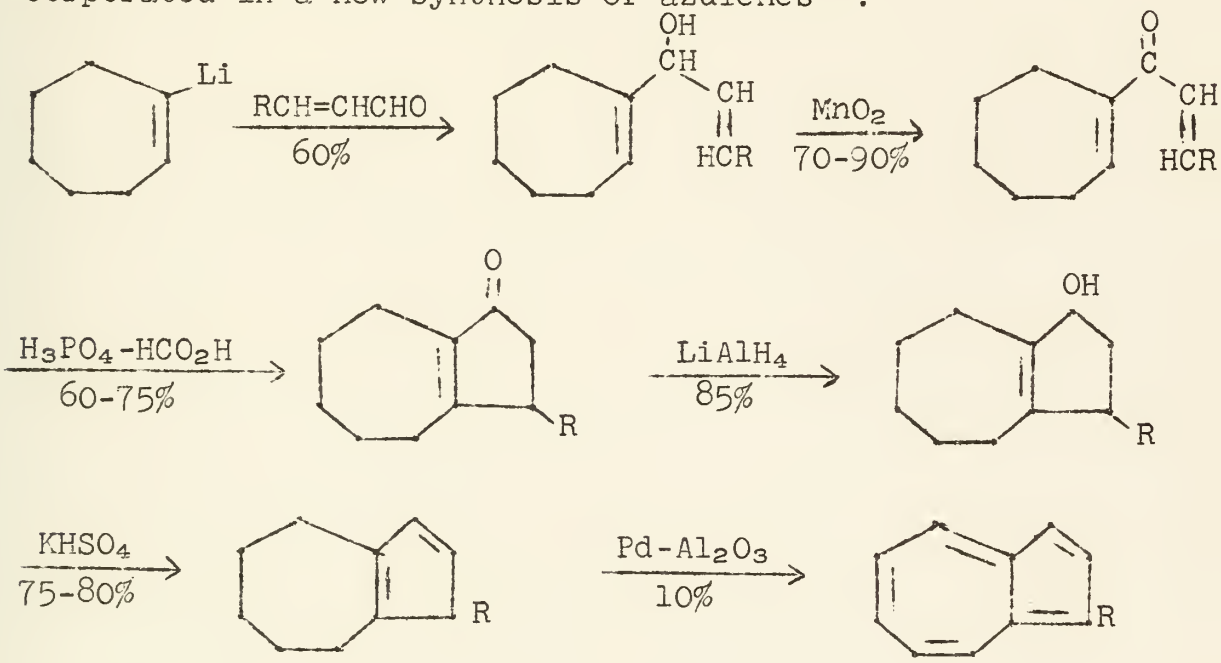
(XI)



(XII)

reactive toward lithium, although 1-chlorocycloheptene is metallated with comparative ease[10].

The use of cycloheptyl-lithium has recently been incorporated in a new synthesis of azulenes[16].



Alkenylation with lithium alkenyls has proved useful in synthesizing unsaturated alcohols, ketones, acids and hydrocarbons which are not easily accessible by other means.

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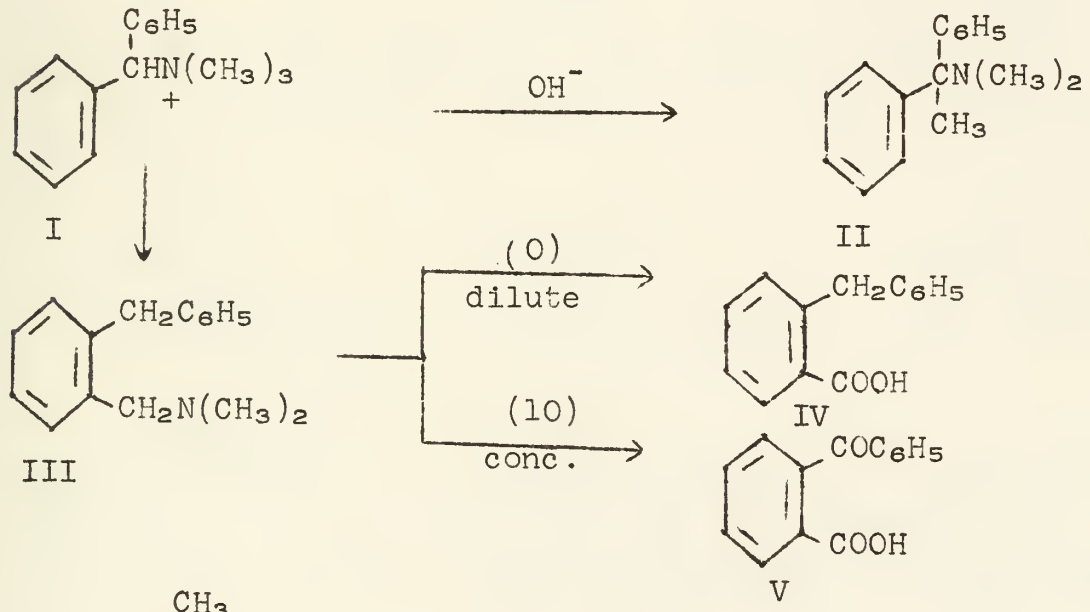
BASE-CATALYZED REARRANGEMENTS OF BENZYL AMMONIUM IONS

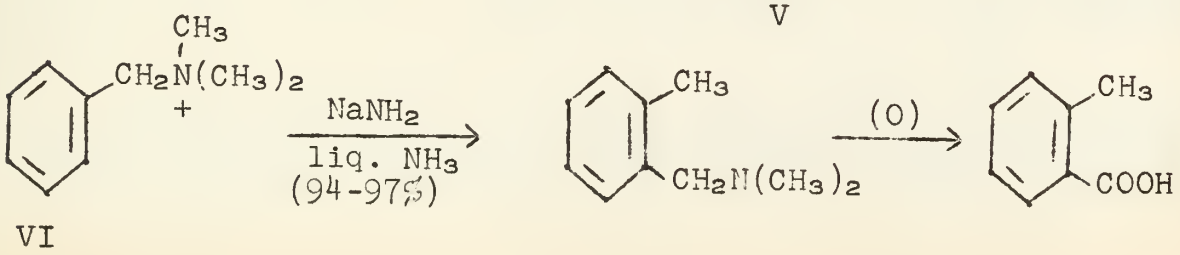
Reported by Joseph J. Ursprung April 30, 1954

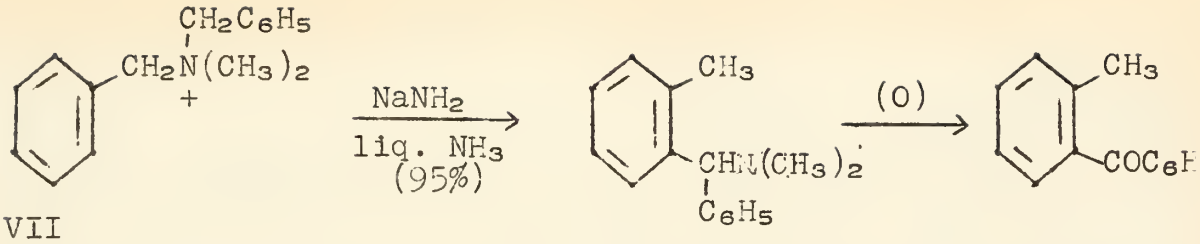
A quaternary ammonium ion may be attacked by a base at three different positions, (a) at an α-carbon to effect the displacement reaction, (b) at a β-hydrogen to give β-elimination, and (c) at an α-hydrogen to form a carbanion. This carbanion may undergo alkylation, β-elimination or rearrangement. This seminar will be directly concerned only with rearrangement of the carbanion formed when a benzyl quaternary salt is attacked by a base.

The first example of a rearrangement was observed by Stevens[1] who found that quaternary ammonium ions and sulfonium ions[2] rearranged in the presence of a strong base to give tertiary amines. Bases which have been used for the Stevens rearrangement include phenyl lithium, fused sodium methoxide or sodium amide and hydroxyl ion.

Several years later Sommelet[3] observed that the quaternary ion I, on treatment with hydroxyl ion, gave not only the Stevens 1,2-shift to II, but also, under speciallized conditions, a tertiary amines (III) in which migration to the ring had occurred. The rearrangement was confirmed by Wittig and his coworkers[4] who further reported that migration could also be effected with phenyl lithium. Kantor and Hauser[5] obtained exclusive migration into the ring when the iodide of I was treated with sodium amide in liquid ammonia. The structure of the product was determined by its direct synthesis and by permanganate oxidations to the known carboxylic acids IV and V. Other examples of rearrangement were soon discovered.





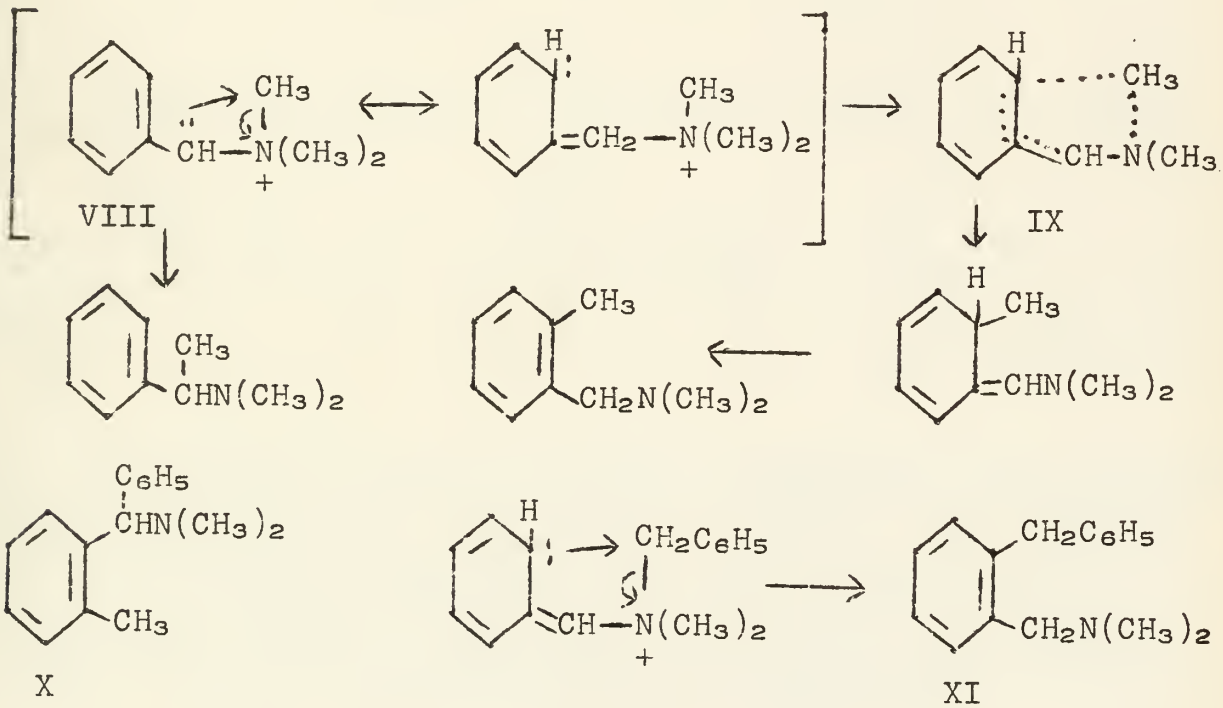


VII

Exclusive migration into the ring with sodium amide in liquid ammonia is rather remarkable, especially since the chloride of VII has been known to give only the Stevens 1,2-shift with fused sodium amide at 140-150°[6]. Rearrangement of I and VII required a large excess (100%) of reagent for maximum yields. This might be expected since the products are diphenylmethane derivatives which, like diphenylmethane, were probably converted partially to their carbanions by the excess sodium amide.

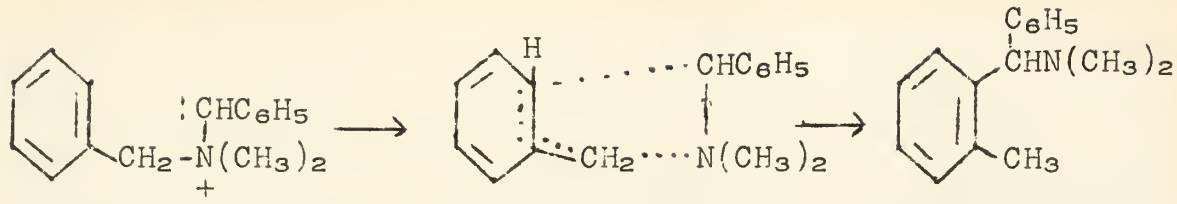
The first step in the rearrangement is undoubtedly the abstraction of an α-hydrogen atom by the amide ion. It has been shown that the Stevens rearrangement involves an intramolecular three-atom ring displacement within an intermediate carbanion[7] such as VIII. A similar mechanism may be written for rearrangement to the ring proceeding through the transition state IX (mechanism 1). However, this does not explain the products formed from I and VII, which, according to this mechanism, would be expected to give products X and XI respectively, contrary to experimental findings.

MECHANISM 1



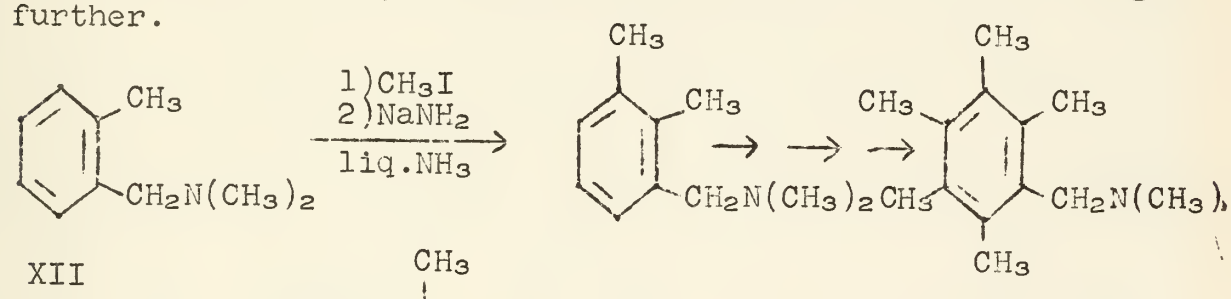
On the other hand, all three rearrangements may be accounted for by an intramolecular rearrangement in which the amine moiety migrates to the ortho position on the ring (mechanism 2)

MECHANISM 2

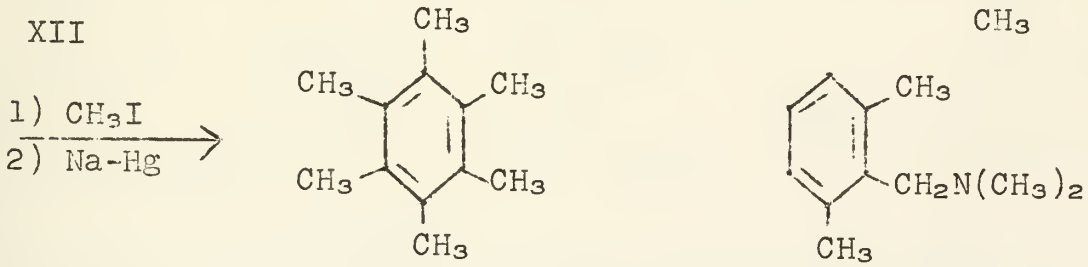


VIII

Further migrations into the ring may be accomplished readily by successive rearrangements following quaternary salt formation with an alkyl halide. Successive o-alkylations of this type furnish striking support for the second mechanism, since, had the first mechanism been operative, the quaternary ion XII would have given XIII which could not have rearranged further.

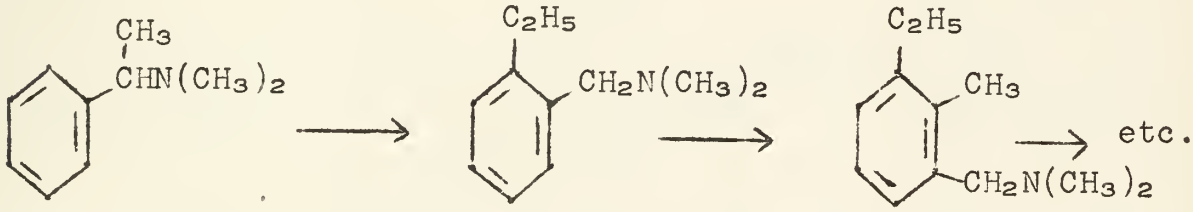


XII



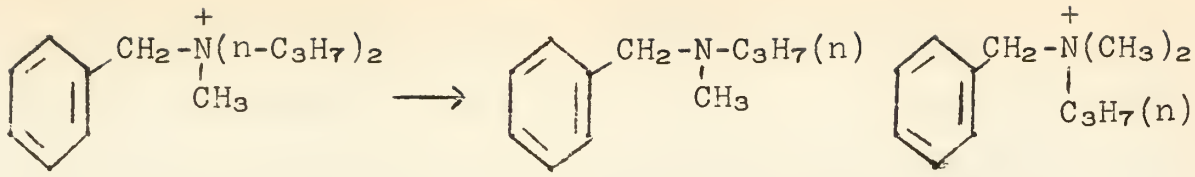
XIII

Hauser has extended the reaction to include alkyl ethylbenzenes.



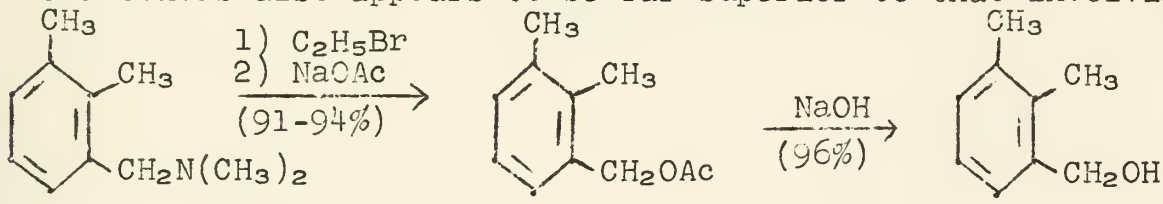
XIV

It seems likely that certain other α-alkylbenzyl trialkylammonium ions could similarly be rearranged to form the corresponding o-alkylated products. β-Elimination, however, is a competing reaction whenever β-hydrogens are present. The quaternary ion XV undergoes 70% β-elimination while the ion XVI gave the elimination product in 40% yield at -33° and in 30% yield at -70°. Likewise the ion XIV gave 14% styrene by a β-elimination, although the main reaction was that of o-alkylation.

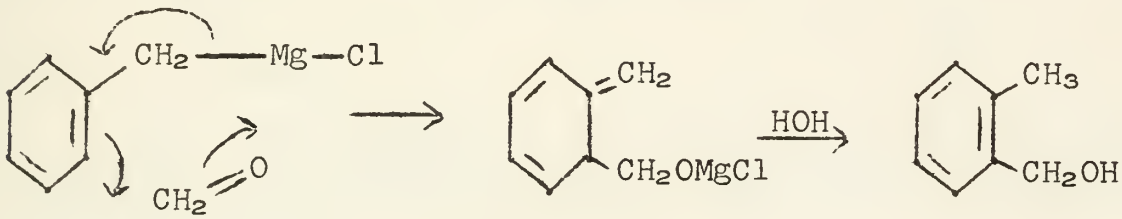


XV + CH_2=CH-CH_3 XVI

While the Stevens rearrangement may be used successfully in the preparation of a wide variety of tertiary amines, the o-alkylation reaction has many applications in the synthesis of vicinal alkyl aromatic derivatives, which are sometimes very difficult to prepare by direct alkylations. The tertiary amines obtained by rearrangements to the ring may be converted in good yields to o-substituted carboxylic acids on oxidation, and to hydrocarbons by reduction with sodium amalgum[9]. Vicinal alkylated benzyl alcohols may be conveniently prepared by this method. The older procedure of decomposing the quaternary hydroxides thermally is somewhat unsatisfactory. Hauser[10] has obtained excellent yields in an S_N2 displacement of the amine residue with acetate ion to give the acetate which can readily be saponified to the benzyl alcohol. This method of preparing the alcohols also appears to be far superior to that involving



the "abnormal" Grignard reaction[11] which gives lower yields, in general, and products contaminated with the "normal" Grignard product.



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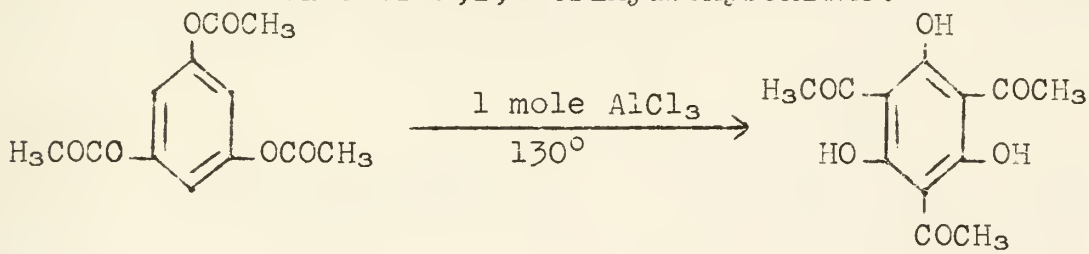
THE FRIES REARRANGEMENT. RECENT DEVELOPMENTS

Reported by Edward P. Merica April 30, 1954

Blatt, in his reviews of the Fries rearrangement[1,2], regarded the mechanism of the rearrangement as unsettled, and also recommended a further investigation of the rearrangements of esters of di- and trihydroxyphenols. This seminar will consider the recent progress made in both of these categories, particularly in the past three years.

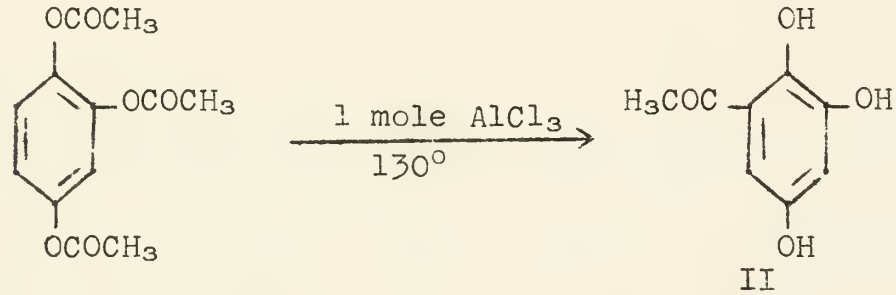
I. Rearrangements of Di- and Trihydroxyphenols

In 1912 Heller reported the preparation of 4,5-diacetylpyrogallol from pyrogallol triacetate by heating the latter at 145° with 1 mole of $ZnCl_2$. At about the same time, Heller[3], Mauthner[4,5] and Rosenmund and Lohfert[3] obtained (I) from the Fries rearrangement of phloroglucinol triacetate and (II) from the triacetate of 1,2,4-trihydroxybenzene:



(1)

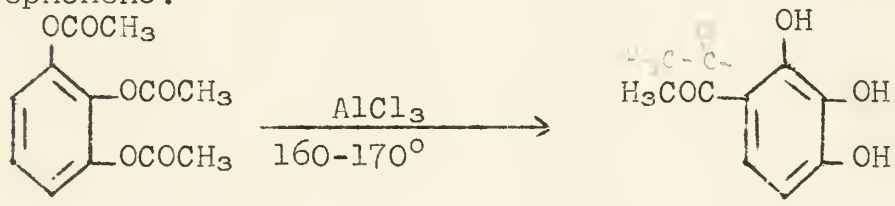
I



(2)

II

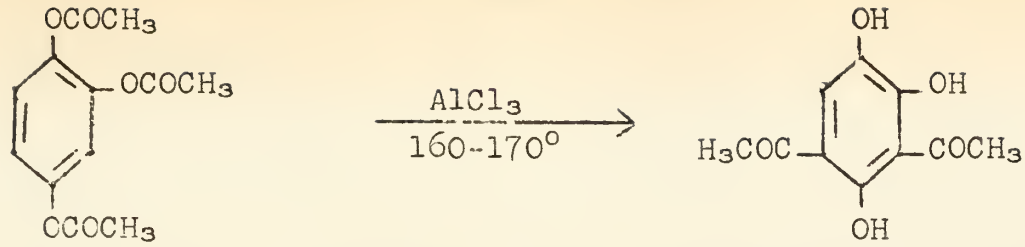
These rearrangements were carried out at moderate temperatures. Desai and Mavani have studied them at higher temperatures[7]. At 160-170° pyrogallol triacetate gave mainly gallacetophenone:



(3)

At 130-140° more than half of the pyrogallol triacetate remained unchanged. The formation of 4,5-diacetylpyrogallol reported by Heller was not encountered.

The triacetate of phloroglucinol gave, at 160-170°, a mixture of triacetyl, diacetyl and monoacetyl phloroglucinols of which the triacetyl derivative was the main component. At 27° smaller amounts of the same products were obtained, along with considerable unchanged starting material. The triacetate of 1,2,4-trihydroxybenzene gave 3,5-diacetyl-1,2,4-trihydroxybenzene at 160-170°:

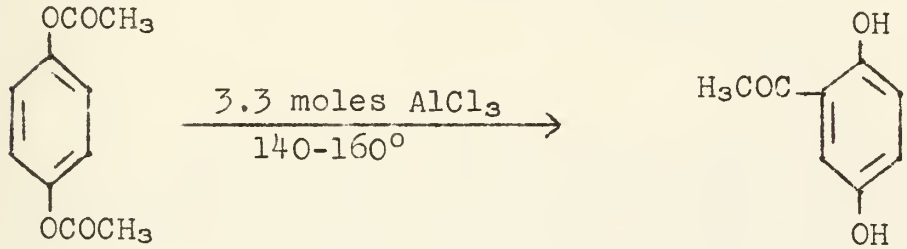


(4)

But at 27° the monoacetyl compound was obtained, in conformity with Mauthner.

Thus, it appears that pyrogallol triacetate gives only the monoacetyl derivative and phloroglucinol triacetate gives only a mixture consisting principally of the triacetyl derivative, whereas it is possible to obtain the mono- or the diacetyl compound from 1,2,4-trihydroxybenzene, depending on th temperature.

Heller found that hydroquinone diacetate did not undergo a Fries rearrangement under the usual conditions[3], but Amin and Shah, using 3.3 equivalents of $AlCl_3$, prepared quinacetophenone (III) and quinpropiophenone[8]:



(5)

III

The study which these authors made of the reaction under various conditions is summarized in the following table.

Exp.	Temp.	Time	$AlCl_3$*	Solv.	Products unchanged diacetate	quinacetophenone
1	20-25°	24 hr.	3.3 eq.	$PhNO_2$	--------	-------
2	85-90°	4	3.3	none	3.0 g.	-------
3	120-130°	4	3.3	none	2.5	0.5 g.
4	140-160°	4	3.3	none	--------	2.7
5	170-180°	4	3.3	none	--------	1.5
6	140-160°	4	3.3	$PhNO_2$	--------	-------
7	140-160°	4	3.3	CS_2	--------	2.1
8	140-160°	4	2.2	none	2.5	-------
9	140-160°	4	1.1	none	3.1	-------

*In each experiment 5.0 g. of hydroquinone diacetate was used.

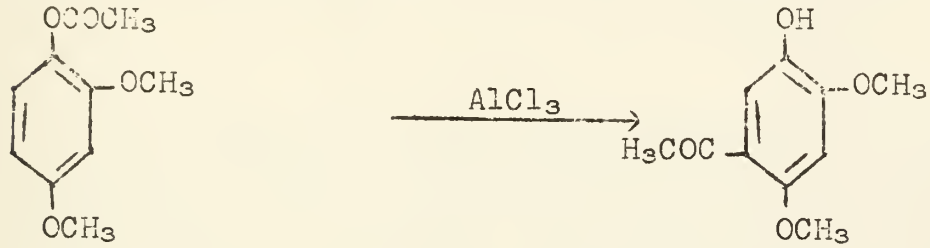
A short time later Desai and Mavani used a higher temperature and shorter reaction time to prepare quinacetophenone and quinpropiophenone, each in 60% yield, and also quinbenzophenone in 50% yield.

II. Mechanism

The principal question to be answered is whether the Fries rearrangement is intermolecular, as proposed by Rosenmund and Schnurr and Skraup and Poller, intramolecular, as proposed by Fries and v. Auwers, or both, as suggested by Baddar and El Assal, who began investigating this possibility in 1950 but have not yet published any results[10-13].

A. Intramolecular

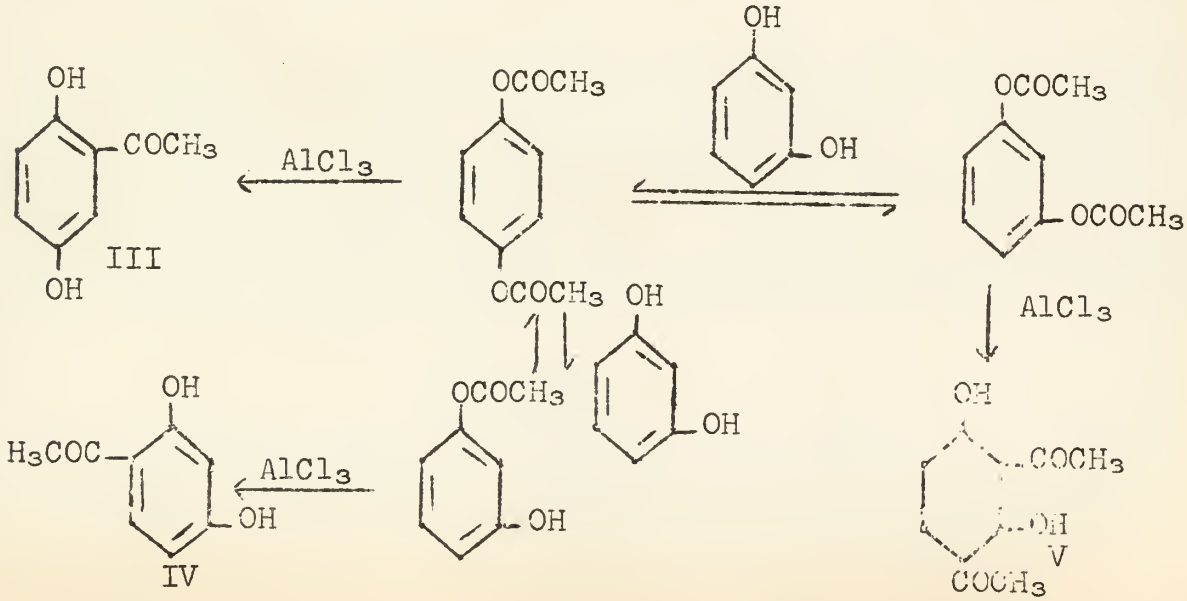
The fact that meta isomers were not formed in the Fries rearrangement while they are in the corresponding Friedel-Crafts synthesis was taken as evidence of intramolecular rearrangement, but Reichstein obtained a meta-hydroxy ketone from guaiacol acetate[14] and Ballio recently prepared the meta product from 2,4-dimethoxyphenyl acetate in 50% yield[15]:



(6)

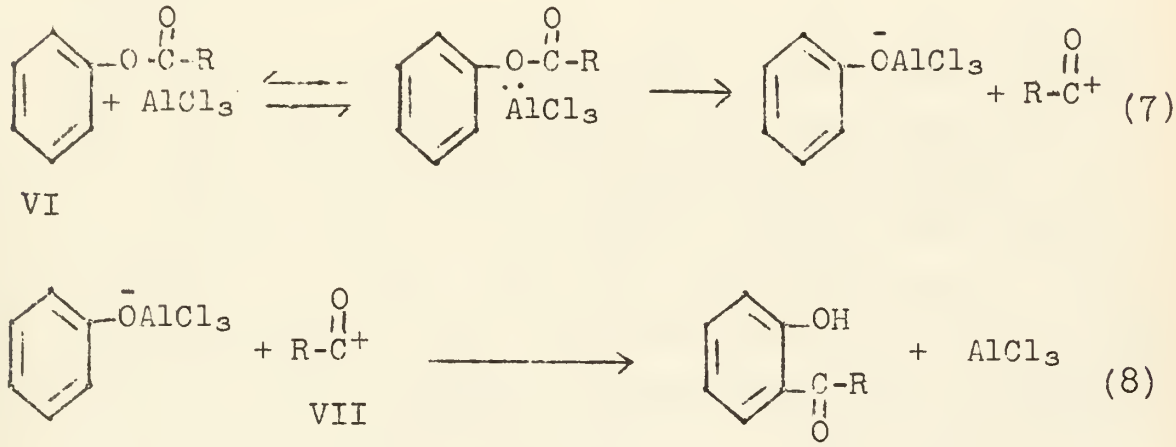
He also obtained meta isomers from 4-methyl-2-methoxyphenyl acetate (8%), 2-methyl-4-methoxyphenyl acetate (1.4%) and 2,4-dimethylphenyl acetate (0.5%)[16]. These yields confirmed Reichstein's view that the migration of the acetyl group is influenced by the orienting action of other substituents.

Desai and Mavani heated a mixture of hydroquinone diacetate, resorcinol and $AlCl_3$ at 160-170° and obtained resacetophenone (IV), 2,4-diacetylresorcinol (V) and only a trace of quinacetophenone (III)[7]. The first two products could result from ester interchange followed by intramolecular rearrangement, but a considerable amount of quinacetophenone would be expected also. Since hardly any of the latter was formed, Desai and Mavani concluded that the mechanism is not intramolecular.

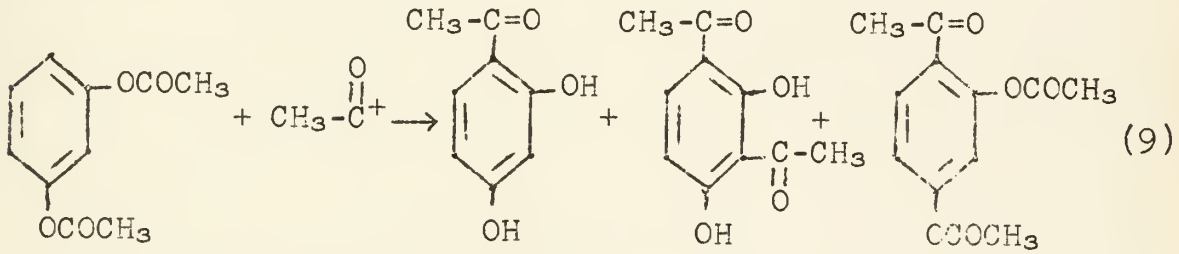


B. Intermolecular

Baltzly and Phillips proposed the following intermolecular mechanism, which is essentially the mechanism of Skraup and Poller expressed in modern terms[17,18]:



The mechanism of Rosenmund and Schnurr involved an attack upon another ester molecule (VI) by the oxo-carbonium ion (VII). Baltzly and Phillips thought it probable that the coordination of the ester (VI) with $AlCl_3$ is practically complete when the latter is in excess, so that the free ester is unavailable as an intermediate. However, when Desai and Mavani heated resorcinol diacetate with $AlCl_3$ a mixture of resacetophenone, 2,4-diacetylresorcinol and resacetophenone diacetate was obtained[7]. The last substance probably was initially formed by the acylation of one molecule of resorcinol diacetate:



Thus the mechanism of Rosenmund and Schnurr was supported.

Chief evidence for the intermolecular mechanism has been the formation of cross-products in mixed Fries rearrangements. Recent examples are the rearrangement of phenyl acetate in the presence of toluene or methoxybenzene, yielding p-methylacetophenone and p-methoxoyacetophenone, respectively, in addition to the expected products[19], and the reaction between phenyl hydrogen succinate and $AlCl_3$ in the presence of toluene which gives rise to both β-o-hydroxybenzoylpropionic acid and β-o-toluoylpropionic acid[13].

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SOME CHARACTERISTICS OF 5- AND 6- MEMBERED RINGS

Reported by Richard C. Thamm May 7, 1954

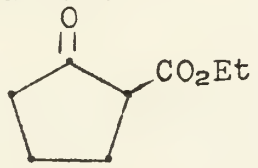
In previous papers by H. C. Brown[1,2] the effect of I-strain has been utilized to explain differences in reactivity of various sized rings at a point on the ring and has been adequately reviewed in a former seminar[3]. Considering the data in Table I with relation to 5- and 6-membered rings alone it will be seen that reactions involving a change in co-ordination number of a ring atom from three to four proceed rapidly in the cyclohexane compounds and slowly in the cyclopentane derivatives; i.e. in the 5-membered ring the trigonal structure for one of the atoms is strongly favored over the tetrahedral arrangement, while in cyclohexane compounds, the exo trigonal structure is less stable.

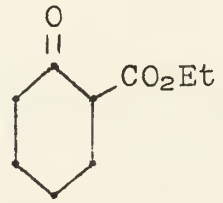
TABLE I - Relative rates

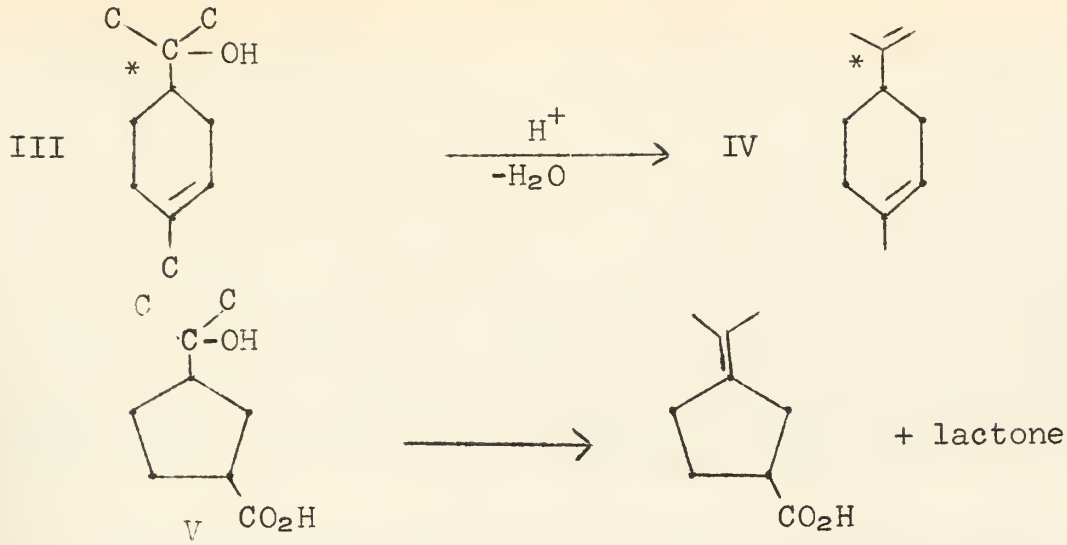
Reaction	Compound Cyclopentyl	Cyclohexyl	Ratio $\frac{\text{6-Ring}}{\text{5-Ring}}$
$>C=O + HCN \longrightarrow >C(OH)CN$	67.1	1087	16
$>C=O + NH_2NH_2CONH_2$	0.0153	0.512	30
$>C=O + C_6H_6CO_3H$	17.3	106	6
$>C=O + H_2$	0.918	6.6	7

Assuming that the differences in stabilities between double bonds exo to the 5- and 6-membered rings is greater than between the endo double bonds, (thermodynamic justification later in abstract) the following generalization is advanced by Brown[4]: reactions will proceed in such a manner as to favor the formation or retention of an exo double bond in the 5-ring and to avoid the formation or retention of the exo bond in the 6-ring system.

Many examples exist in support of this view. For example the carbethoxy derivatives (I and II) exist in the enol form to the extent of 5% and 57% respectively in 95% ethanol as determined by potentiometric bromine titration[5]. This again illustrates that the double bond is less stable in cyclohexane when exo to the ring. Isomerization data of 5- and 6-membered rings strongly indicate that the rule is valid[4]. Perhaps the most striking observation is one made by Flawitsky[6], that in the dehydration of α-terpeneol (III) the <u>optically active</u> limonene (IV) is obtained as product. On the other hand, the carboxylic acid derivative (V) gives the exo double bond when dehydrated[7].

I 

II 



The generalization does not appear to be useful in the fused ring systems, although it may be applicable in predictions concerning the Mills-Nixon effect[8].

In the aqueous hydrolysis of γ-butyrolactone (five membered) and δ-valerolactone (six membered), both having exo double bonds, the equilibrium concentrations of lactone are 72.8% and 9.0% respectively, basic hydrolysis of the δ-ring occurring at a rate 22 times that of the γ-derivative[9]. In contrast, the cyclic acetals of γ-hydroxybutyraldehyde and δ-hydrodyvaleraldehyde (no double bonds) exist at equilibrium to the extent of 88.6% and 93.9% respectively[10]. This demonstrates the remarkable influence of an exo double bond upon the stability of usually more stable six-membered rings. In addition, this explains why the sugar acid lactones prefer the 1,4 (γ)-form while the 1,5- or pyranose-form of the sugar aldehydes is most common.

On the basis of existing thermochemical data it is possible to support, in some measure, the generalization as stated, including the reservation made in its formulation[4].

TABLE II

Compound	ΔH_f	ΔH_{H_2}	Increment $(\Delta H_{f(g)} - \Delta H_{f(s)})$
cyclopentane	-18.46		
cyclohexane	-29.43		-11.0
cyclopentanol	-59.3		
cyclohexanol	-70.5		-11.3
cyclopentanone	-47.2	-12.50	
cyclohexanone	-55.6	-15.42	- 8.4
cyclopentene	7.87	-26.92	
cyclohexene	- 1.70	-28.59	- 9.6

In Column 2 of Table II some of these data have been summarized by Brown, and the following arguments advanced: The difference in the heats of formation of cyclopentane and cyclopentanol is 40.8 kcal., a value almost identical with the difference between cyclohexane and cyclohexanol (41.2 kcal.). Replacement of one hydrogen by hydroxyl has not introduced any significant differences in energy between the two series.

However, the difference in heats of formation of cyclohexane and cyclohexanone is 26.17 kcal. as compared to a change of 28.74 kcal. for the corresponding cyclopentane compounds. This indicates that the double bond of cyclohexanone is less stable than that of cyclopentanone by an amount corresponding to 2.6 kcal. The difference between propane (-24.82) and acetone (-51.8) is 27.0 kcal., a value intermediate between the calculated values of 26.2 and 28.2 for the cyclopentane and cyclohexane derivatives, respectively; this would indicate that the difference in strain results from both a decrease in strain going from cyclopentane to cyclopentanone and an increase in strain proceeding from cyclohexane to cyclohexanone. These same conclusions are reached in considering the heats of hydrogenation of the cyclic and acyclic ketones.

As mentioned in the formulation of the postulate, it is necessary to assume that the difference between the stabilities of the exo double bonds is greater than that for the endo double bonds in the 5- and 6-membered rings. In the absence of good heat of formation and heat of hydrogenation data for the two cyclic methylene compounds, it is necessary to resort to information on the two ketones. From Column 3 of Table II it is seen that the heats of hydrogenation for the two ketones differ by 2.92 kcal., while the olefins differ only by 1.67 kcal. This at least sets a lower limit upon the relative stabilities of the exo and endo bonds in the two rings. Heats of combustion data on the isomeric (endo-exo) unsaturated compounds in the cyclohexane series[11] strongly indicate that the difference may be even greater when good work is finally presented for the cyclopentane compounds of the same type.

The available double bond absorption data for model compounds in this series are included in Table III (R indicates Raman spectra, others being infrared).

TABLE III

cyclohexene[12]	*1654 (R)	methylene cyclohexane[12]	1651 (R)
cyclopentene[12]	1611 (R)	methyene cyclopentane[12]	1657 (R)
1-heptene	1642 (R)	methylene cyclobutane[13]	1679 (R)
cyclohexanone	1710	methylene cyclopropane[14]	1723-1785
cyclopentanone	1740	2-methyl cyclohexene[12]	1676 (R)
cyclobutanone	1775	2-methyl cyclopentene[12]	1656 (R)
		2-methyl cyclobutene[13]	1641 (R)

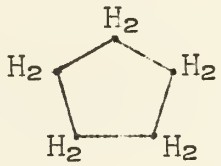
*Wave number

It will be noticed that in any one series, changes in frequency are uniform in proceeding from the largest ring to the smallest. In the cyclic ketone series, for example, there is an increase in frequency in going from cyclohexanone to the smaller rings. This in turn denotes an increase in the magnitude of the force constant for the double bond. Similarly, the force constant of the double bond in methylene cyclopentane is greater than that in the cyclohexane compound. Unfortunately, it is difficult to make direct use of these data in correlation of endocyclic vs. exocyclic bond re-

activities, since these are usually functions of both the transition state and the ground state.

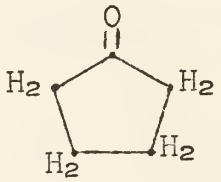
In discussing the theoretical implications which might be derived from the forgoing material, Brown has suggested that "the effect of the carbonyl in stabilizing the cyclopentane ring can be attributed to a decrease in the number of bond oppositions" whereas an introduction of an exo double bond to the cyclohexane ring destroys the completely staggared configuration and introduces some measure of unfavorable conformations (see figures VI - IX). However, as he carefully points out, the alpha hydrogens may not be essential for strained conformational effects since lactones (only one alpha methylene group) and both the ethylene and trimethylene carbonates show this same influence of ring size upon stabilit Here it is postulated that it is the two lone electron pairs on the alpha oxygen atoms which produce the conformational effect. If the above reasoning holds, then this also is not unreasonable since the potential barrier to rotation in dimethyl ether is 2700 cal. as compared to 3400 cal. reported for propane, there being only a slight difference between the two.

VI

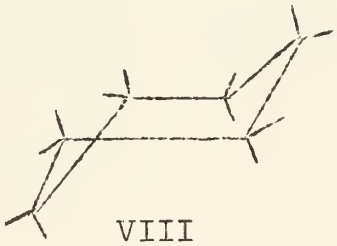


10 oppositions
10 kcal. strain

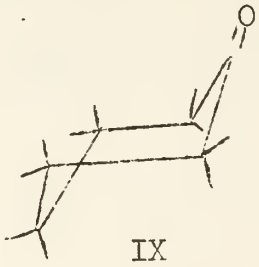
VII



6 oppositions
6 kcal. strain



VIII



IX

However, from the spectral evidence presented in Table II it is apparent that differences in bond reactivities cannot be attributed to these effects alone, since exo bonds in the two series possess different degrees of hybridization.

It has been suggested by Schwarzenbach[15] that the low per cent enolization of acetoacetic ester in water may be due to an entropy factor. That is, in going to a state of fewer degrees of freedom there should be a negative entropy change. There are two pieces of evidence which fail to support this view: (1) Brieglieb and Strohmeier[16] have shown that at least in the case of acetylacetone, ΔS is small with respect to ΔH; (2) as has been shown, 2-carbethoxy cyclohexanone (II) is enolized to a greater extent than the corresponding cyclopentanone derivative - a situation which we should expect to be reversed if the above hypothesis were true.

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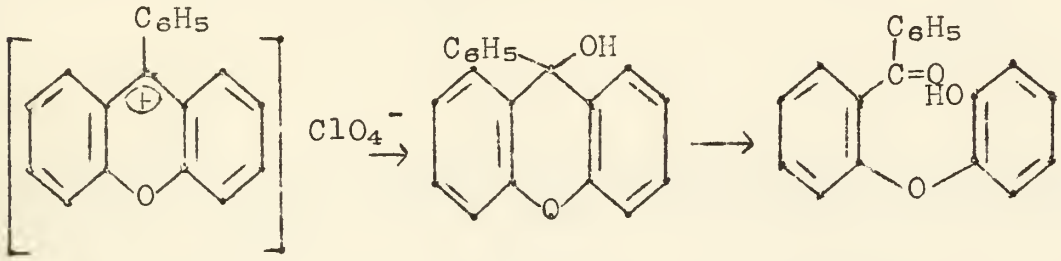
ORTHO- HYDROXYLATION OF PHENOLS

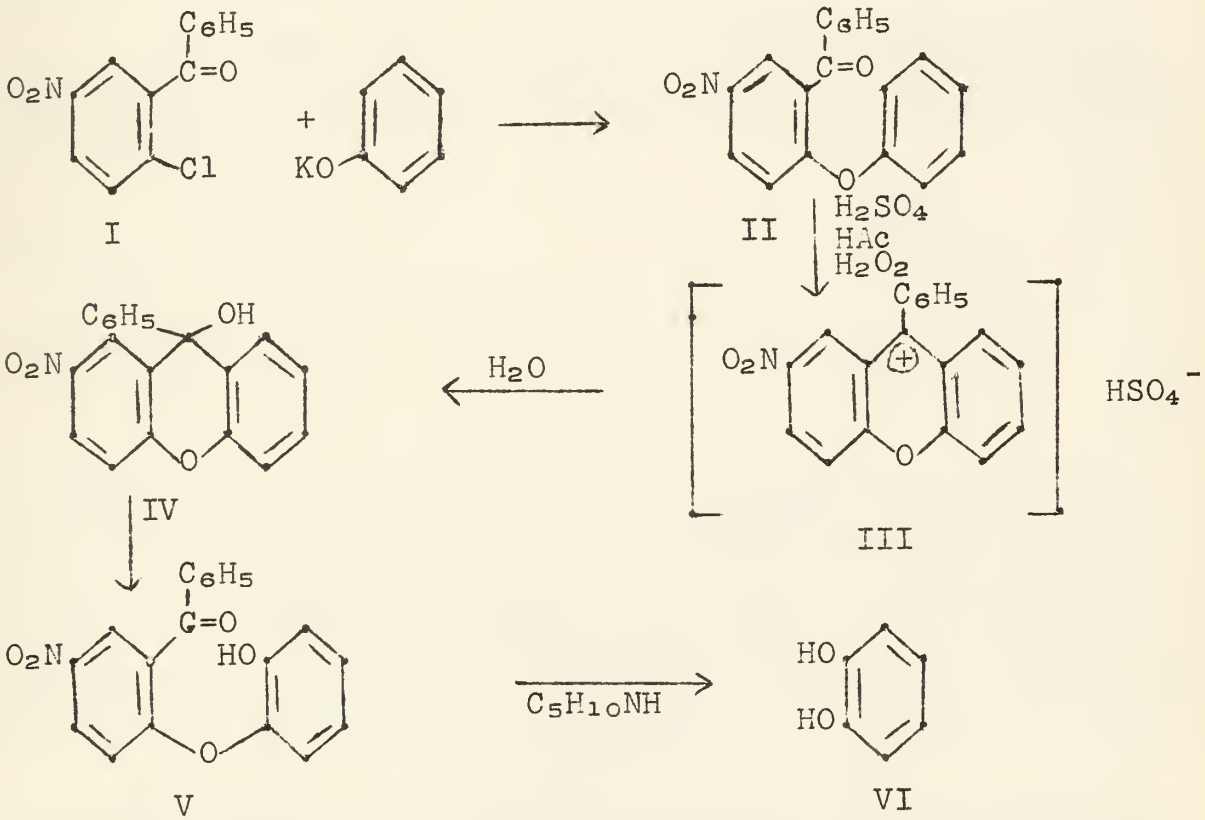
Reported by S. A. Aspey May 7, 1954

It was reported, in 1931, that 9-phenyl xanthylium perchlorate upon oxidation with hydrogen peroxide in acetic acid yielded 2-(2"-hydroxyphenoxy-)benzophenone[1]:



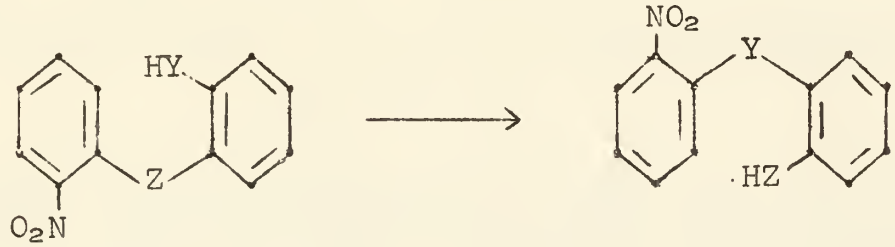
Although some related compounds gave neutral products, presumed to be peroxides, others gave catechol derivatives by means of oxidation of the xanthhydrol in sulfuric acid-acetic acid. Phenol, o-, m-, and p-cresol gave almost quantitative yields of the respective catechol. Liberation of the catechol from its aryl ether was not extensively examined. However, the scission of o- and p-nitrated diaryl ethers by piperidine had been previously reported.[2,3]

Loudon and coworkers determined to study the reaction further to determine its general applicability and test the possibility of extension to the synthesis of pyrogallols.[4,5,6,7] The general reaction scheme was as follows:

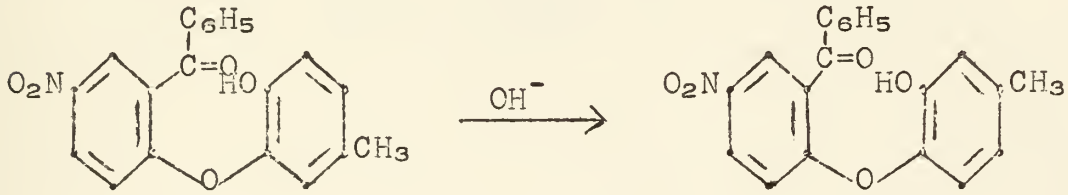


The principal difficulty encountered was the effect of alkaline media - either in the formation of the original ether, if using a catechol derivative, or upon cleavage of the

hydroxylated ether with a base. The problem is an example of the Smiles Rearrangement exemplified by the following and consisting of the migration of the nitrophenyl group from Z to Y[8]:



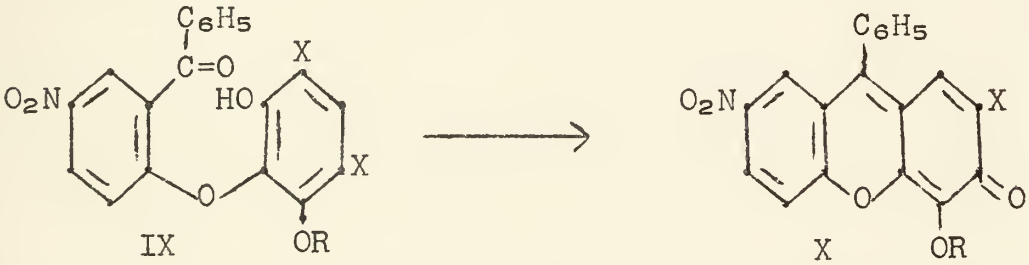
An example in the series under consideration was the almost complete conversion upon dissolving in alkaline solution, of (VII) to (VIII):



VII VIII

Attempts to forestall the migration by methylation of the hydroxy group, following the first hydroxylation, with dimethy sulfate in alkaline solution naturally resulted in migration before alkylation. However, the use of diazomethane was found to be successful.

In extending the synthesis to trihydroxy compounds an additional interfering reaction was found if alkylation was not performed before attempted scission of the ether. This is illustrated by:



where X=H, R=H. It is assumed that migration of the benzophenone radical to the adjacent hydroxy group takes place, followed by cyclization involving the reactive para position of the phenolate ion. Attempts to block the latter phase by bromination were unsuccessful - treatment of (IX) (X=Br) led to the more bromo dehydration product (X) (X=Br) - and similarly with p-cresol. However, starting with 3,5-dimethyl phenol, the intermediate (IX) ($X=CH_3$) was obtained and underwent normal scission with piperidine.

In addition to methylation to prevent group migration under the influence of alkali, formation of the p-tosylate was found acceptable although the acetyl and benzoyl analogues failed to suppress the fluorone formation in the subsequent treatment with piperidine.

The latest paper in the series describes the use of 2-chloro-3,5-dinitrobenzophenone in place of the 2-chloro-5-nitrobenzophenone with the result that the ethers could be prepared at room temperature and cleavage of the ether was found to be better with phenylhydrazine.[7] There was also less tendency towards fluorone-type compound formation.

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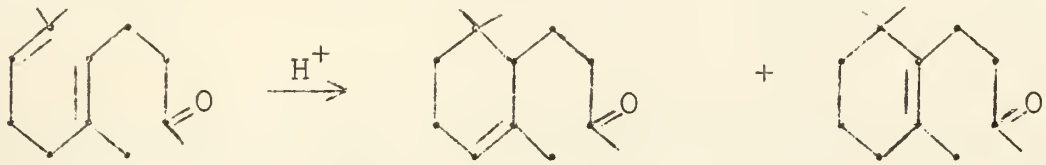
THE ACID-CATALYZED CYCLIZATION OF POLY-OLEFINS

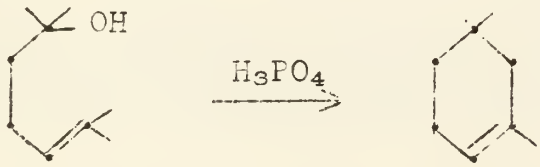
Reported by Richard A. Sneen May 14, 1954

The first example of the cyclization of a poly-olefin was reported in 1893 by Tiemann and Krueger[1] who found that pseudoionone was converted to a mixture of ionones in the presence of concentrated sulfuric acid.

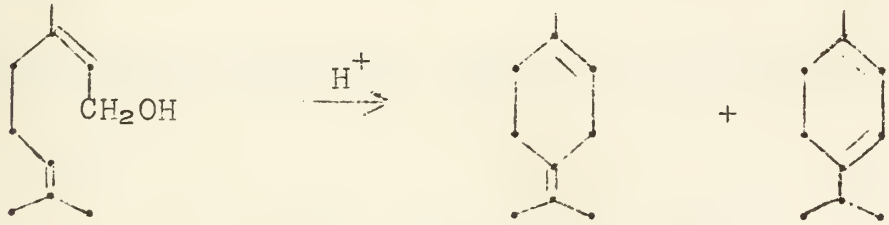


α-ionone β-ionone

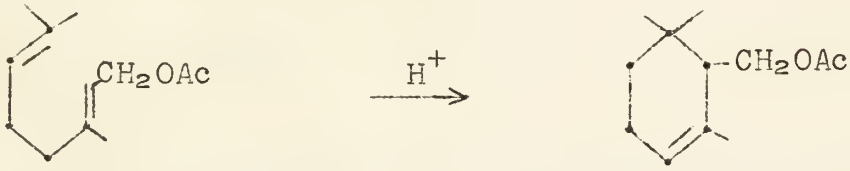
It was later discovered that a similar cyclization occurs with properly constituted unsaturated tertiary alcohols.[2]



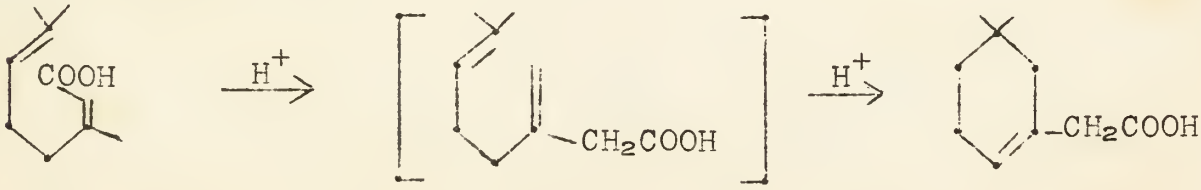
Monoterpenes of three kinds can be formed by this synthetic procedure.[3,4] The production of the first type, compounds with the p-cymene structure, is illustrated by the treatment of geraniol with concentrated acid. The



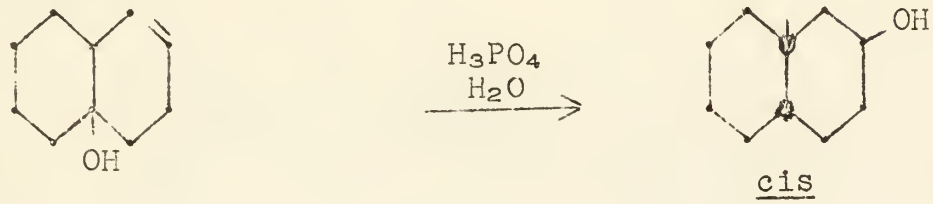
second type, terpenes with a 1,1,3-trimethylcyclohexane skeleton, is illustrated by the formation of cyclogeranyl acetate from geranyl acetate.

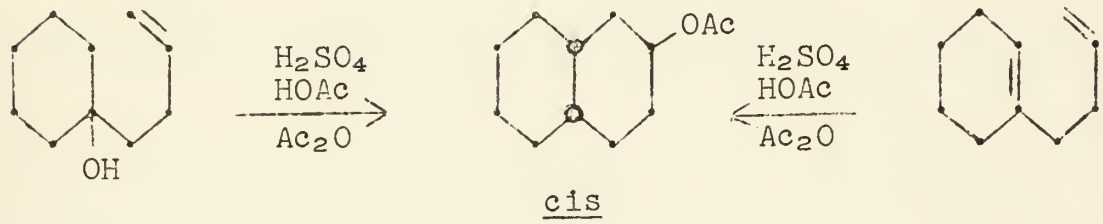


A representative of the third type, allo-cyclogeranic acid, is formed from <u>cis</u>-geranic acid.

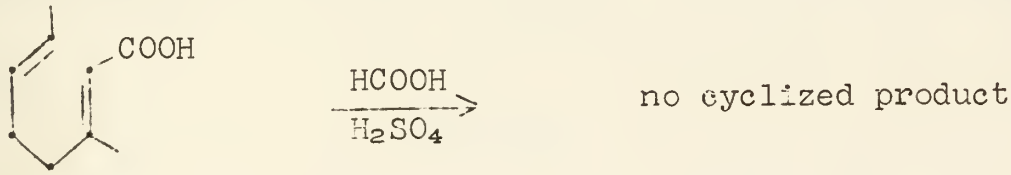


Linstead and his coworkers[5,6] have shown that, in the cases studied, the diene cyclization seems to be stereospecific.

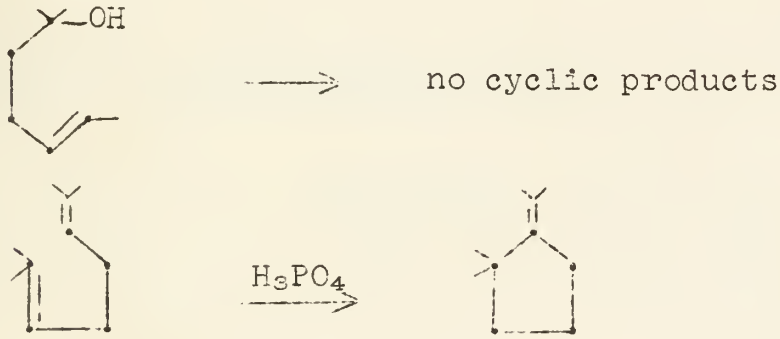




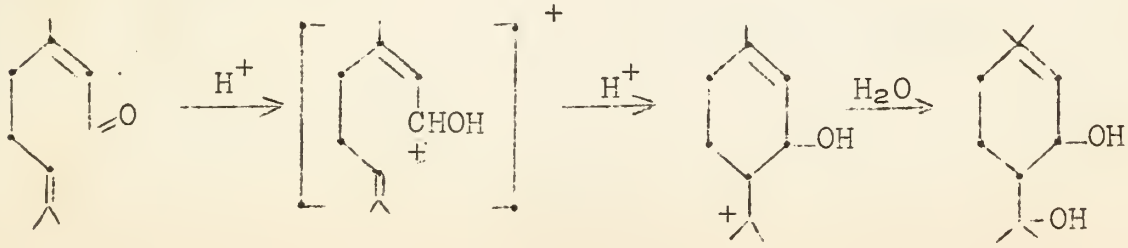
The synthetic utility of the cyclization reaction is severely limited by structural features. The excessively high energy of primary and secondary carbonium ions usually restricts the reaction to systems which do not require such intermediates.



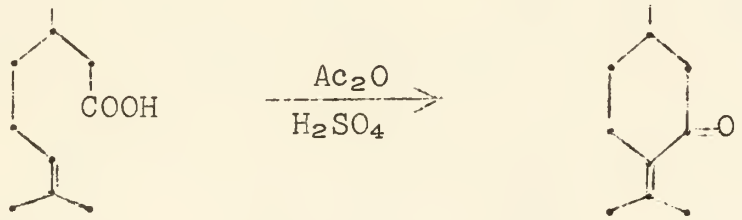
Five-membered rings are formed only if the corresponding six-membered ring is too highly strained.[5,7]



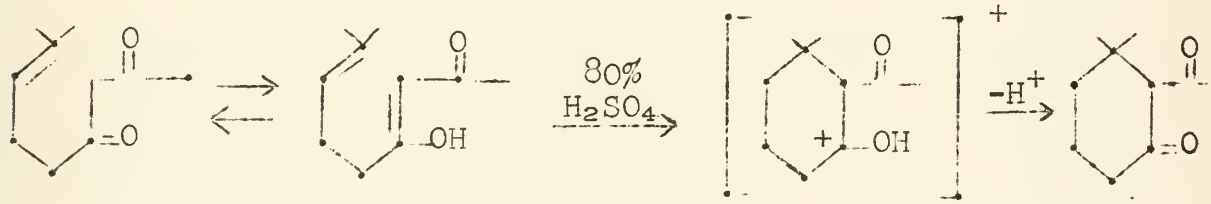
Price and Kickman[8] have interpreted the acid-catalyzed cyclization of unsaturated aldehydes as an internal Prins reaction and have shown that it is formally similar to the diene cyclization.



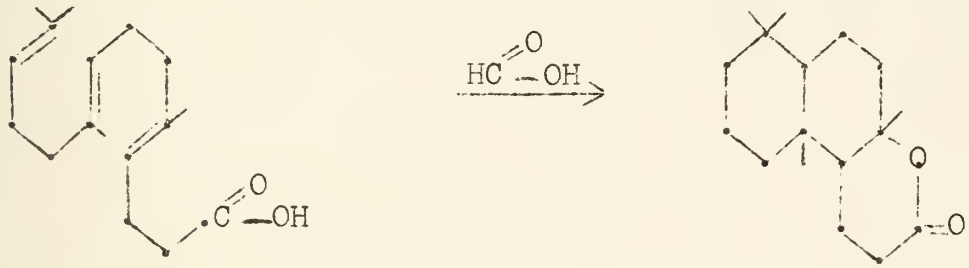
Recently Schinz and his co-workers[9,10] have demonstrated that appropriate unsaturated acids can be cyclized to olefinic ketones in a manner reminiscent of the Friedel-Crafts synthesis.



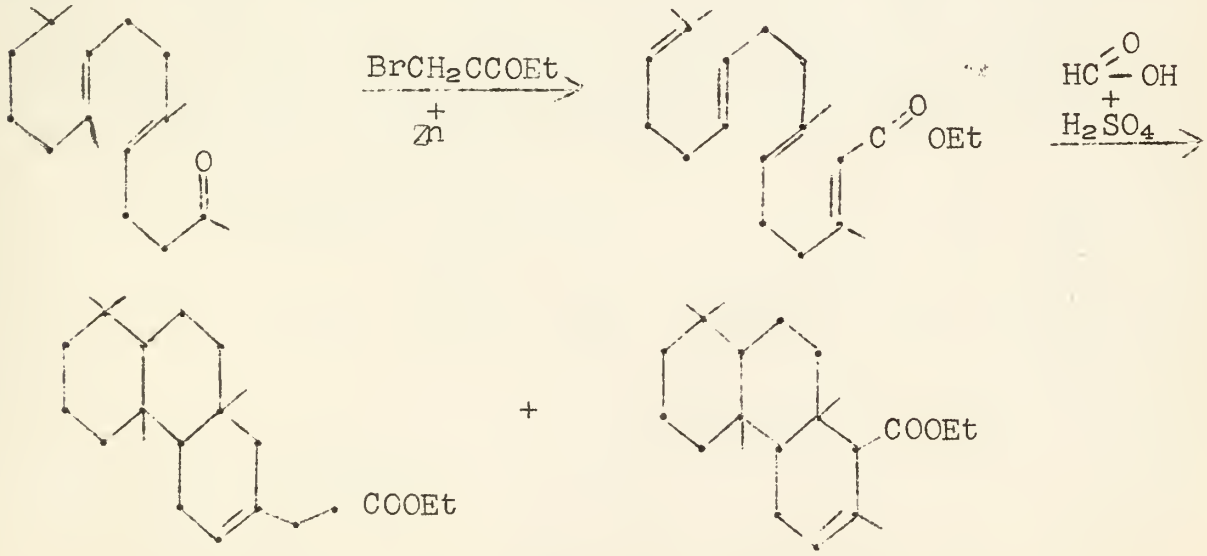
The cyclization of a mono-olefinic ketone has also been effected.[11] The ketone probably reacts in its enol form.



The acid-catalyzed cyclization of poly-olefins is an extremely useful method for the snythesis of complex diterpenes and other polycyclic systems. Dietrich and Lederer[12] have effected a one-step synthesis of ambreinolide.

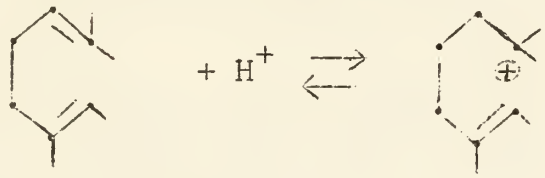


Caliezi and Schinz[13] have synthesized the ethyl esters of two isomeric ω-geranyl-geranic acids.



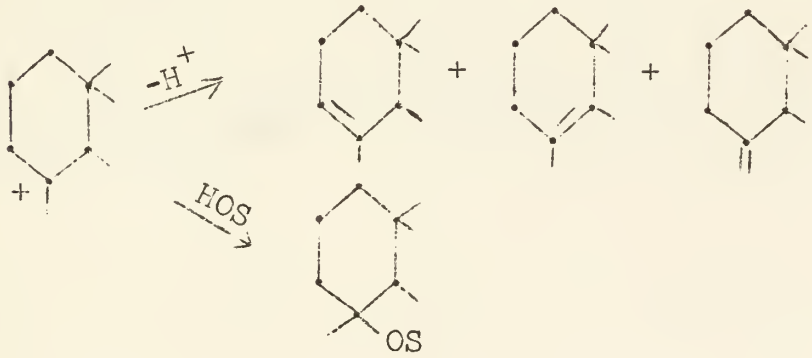
In 1943 Bloomfield,[14] extending the theory of Whitmore,[15] proposed that the acid-catalyzed cyclization proceeds by the initial formation of a carbonium ion (Step I) which then adds to a double bond in the rate-determining step to form a new carbonium ion. (Step II) This intermediate is then stabilized by losing a proton to form a new olefin or by reacting with available nucleophylic species (HOS) to form an alcohol or an ester. (Step III)

I. Carbonium ion formation



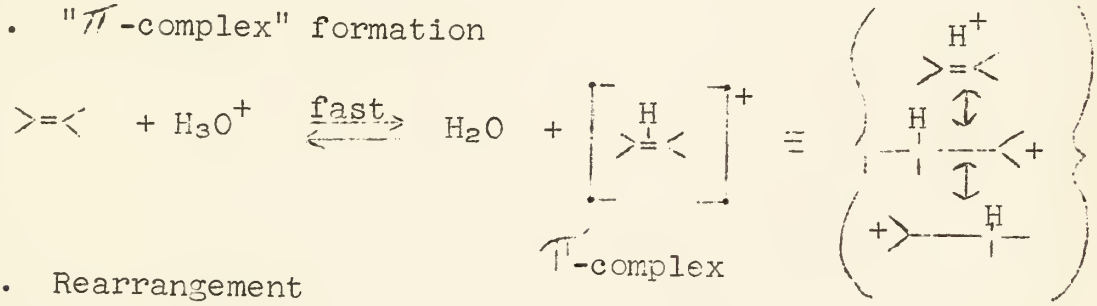
II. Cyclization

III. Stabilization

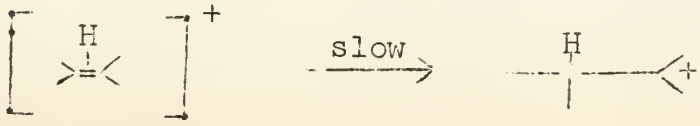


It may be necessary, however, to re-evaluate Bloomfield's mechanism for the cyclization of dienes in terms of the recent findings of R. W. Taft,[16] who has shown that, in the hydration of olefins, the rate-determining step is the rearrangement of a "π-complex"[17] to a classical carbonium ion. (Step II) The stereochemistry of the olefin is retained until the rearrangement step.

I. "π-complex" formation



II. Rearrangement



If it be assumed that the rearrangement of the "π-complex" proceeds in a concerted fashion it becomes possible to explain the stereospecific trans addition observed in the cyclization of dienes.

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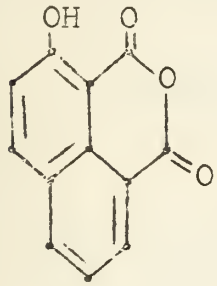
THE CONSTITUTION OF CEVINE

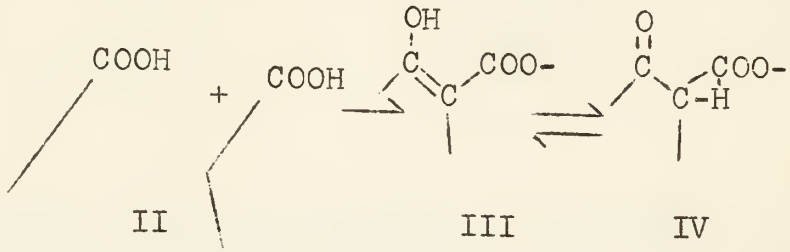
Reported by Lee A. Miller May 14, 1954

The characteristic alkaloids of Veratrum and related species can be divided into two classes, the first of which is composed of a group of C_{27} bases of relatively low oxygen content, which occur free or in glycosidic combination. The second class consists of bases possessing the empirical formula $C_{27}H_{43}NO_n$ (n=7-9). These bases are known as alkamines and are invariably found in nature as esters of simple organic acids.[1] The highly oxygenated alkamines have been widely used in medicine as hypotensive agents.[2] The chemistry of these alkamines, and especially cevine, a base obtained by the vigorous alkaline hydrolysis of the naturally occurring ester alkaloids cevadine, veratridine, and cevacine, has been studied rather intensively for the past fifteen years without marked success. Recently, however, Barton, Jeger, Prelog and Woodward, in a remarkable paper, were able to elucidate a structure for cevine which accounts for all of its known properties.[3]

A very careful study of the oxidation of cevine with chromic and sulfuric acids has been carried out, most of the numerous products being more or less carefully characterized, but not identified.[4] One of the products obtained by this oxidation procedure was a lactone tricarboxylic acid, $C_{14}H_{18}O_8$. Pyrolysis of this substance yielded decevinic acid, $C_{14}H_{12}O_6$. Treatment of decevinic acid with diazomethane resulted in the formation of a dimethyl derivative, while titration with alkali indicated the acid was dibasic in character. 2-Hydroxynaphthalic anhydride (I) was obtained in good yield from decevinic acid by dehydrogenation.[4] The product obtained on dehydrogenation contained two carbon rings, and therefore decevinic acid very likely contained two such rings. The lactone tricarboxylic acid precursor, however, could not contain more than one carbon ring, a limitation imposed upon it by its empirical formula. It is, therefore, necessary to postulate the formation of a carbon-carbon bond during the course of the pyrolysis reaction leading to decevinic acid. A possible course for this reaction is shown in II, III and IV. Structures III or IV might well be present in decevinic



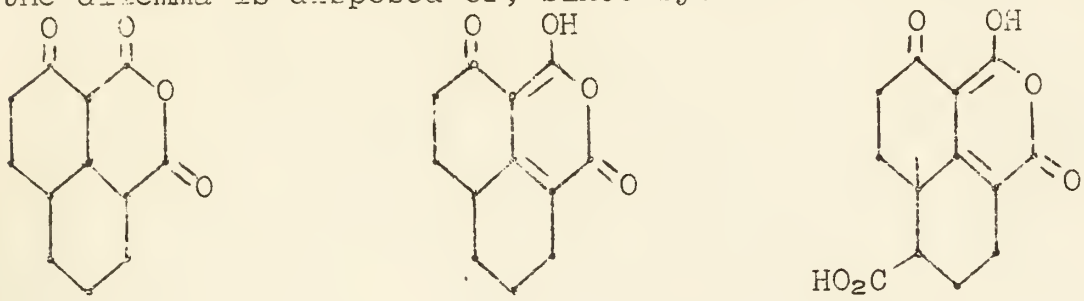
I



II III IV

acid, while II could be a portion of the lactone tricarboxylic acid molecule. By assuming the presence of III or IV in a molecule differing little from I, a tentative structure may be written for decevinic acid (V). It is obvious that the two missing oxygens in V must be present in an acidic system, since a dimethyl derivative was obtained by the action of

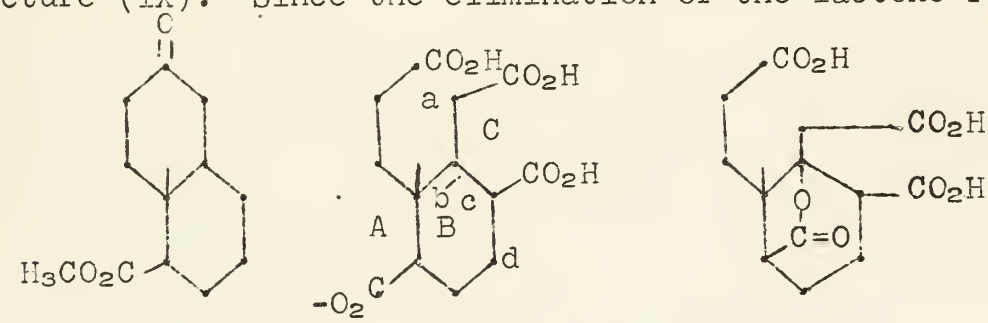
diazomethane on decevinic acid. However, insertion of a carboxyl group in V would require that V be responsible for the take-up of only one mole of alkali, an occurrence which would be very unlikely. If the simple anhydride system is changed to the unique acyl glutaconic system present in VI[3], the dilemma is disposed of, since systems of this sort are



V VI VII

known to behave as strong monobasic acids and are relatively stable towards hydrolytic cleavage.[5,8] The part structure VI differs from decevinic acid by $C_2H_2O_2$ indicating the presence of a methyl group and the previously mentioned carboxyl group in the acid. The carboxyl group has been shown to be attached at C_5 by degradation of decevinic acid to VIII.[7] Since the methyl group is readily lost during pyrolysis, it is placed at the only bridgehead available. All of the known chemical and physical properties of decevinic acid are accounted for by structure VII.[3]

A part structure for the lactone tricarboxylic acid may be postulated from the preceding discussion (IX). If it is assumed that IX arose from a steroid or modified steroid by oxidation, additional confirmation for the attachement of the carboxyl group at C_5 is obtained, since cleavage of ring A between carbons 3 and 4 would lead directly to this type of structure (IX). Since the elimination of the lactone function

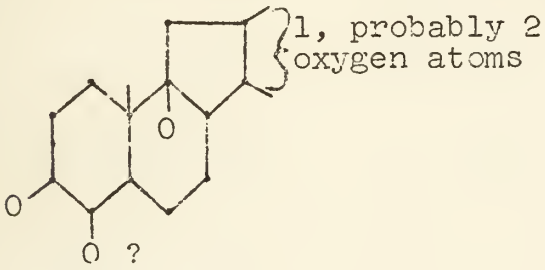


VIII IX X

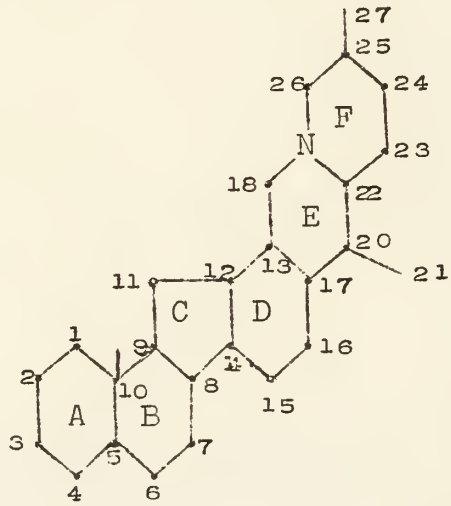
is probably responsible for the generation of the double bond in the acyl glutaconic system present in decevinic acid, the point of attachment of the lactone oxygen atom is limited to carbons a, b, c and d (IX). The possible points of attachment have been further limited to b and d by infrared studies which have shown the lactone ring to be five-membered (band at 1782 cm^{-1}).[7,8] Since attachment at d would require a double bond migration to b-c which would have to proceed through removal of an inactivated hydrogen atom (at b) as a proton, b is the preferred point of attachment. This postulate has been shown to be correct in recent mild

oxidation studies with cevadine[9]. Thus, the complete structure for the lactone tricarboxylic acid may be written as shown (X).

The oxidation studies described above have shown the presence of oxygen at C_3 and probably C_4 in a normal steroid A-B ring system and have also indicated the presence of one further oxygen in the A-B system, probably at C_9. Furthermore, the presence of the $-CH_2CO_2H$ chain in X strongly suggests a five-membered C ring because a normal steroid nucleus would probably undergo oxidative cleavage between C_{11} and C_{12}. These relationships may be shown in figure XI. It is probable that one or two oxygen atoms are attached at the C-D ring juncture, thus facilitating the observed cleavage.[3] Jacobs and Pelletier have postulated XII as the skeleton of cevine. This proposal, accepted by Barton, et. al.[3] as correct, stems from extensive dehydrogenation and correlative studies which appear to be sound.[10]



XI



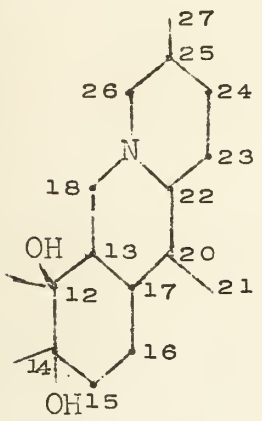
XII

Barton, et.al.[3] have assumed the presence of a secondary α-ketol group in cevine. Perhaps, the most clear-cut evidence in favor of the proposed grouping comes from the basic isomerization of the alkamines veracevine, cevagenine, and cevine.[11,12] Veracevine and cevine differ solely in the configuration of the C_3 hydroxyl group, while cevagenine is an isomeric ketone, such as could be formed through opening of the ketol system. The desirability of attaching oxygen atoms at both C_3 and C_4 of ring A suggests at once that the masked α-ketol system be placed at these positions.[3,13]

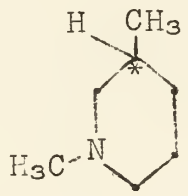
The occurrence in cevine of an independent ditertiary 1,2-glycol system, neither of whose hydroxyl groups are β to nitrogen, has also been demonstrated by Barton, et. al.[3] It has been shown that cevine forms a triacetate, which, although stable to chromic acid (secondary hydroxyl group absent), readily takes up one mole of lead tetraacetate or periodic acid.[14] This indicates the presence of a ditertiary 1,2-glycol system in cevine. Furthermore, neither of the hydroxyl groups can be β to nitrogen since, β-dialkylaminoalcohols react sluggishly with lead tetraacetate[15] while tertiary α-amino ketones consume one or more moles of this reagent at

room temperature.[16,17] Thus, in concurrence with XI, the glycol system must be placed at the C-D ring juncture.[3]

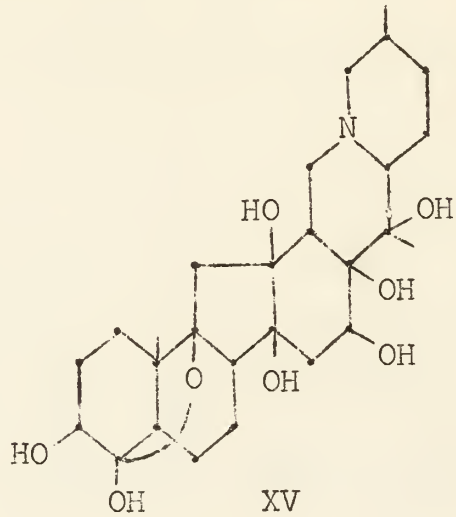
The problem of assigning positions to the three additional hydroxyl groups of cevine, all of which must be attached to the D-E-F system (XIII), still remains. C_{18}, C_{22} and C_{23} may be ruled out since cevine exhibits none of the characteristic properties of an α-carbinolamine. Attachment of hydroxyl at C_{13} or C_{15} would lead to the consumption of more than the observed amount of periodic acid, because these positions are adjacent to the periodate sensitive ditertiary glycol system. Cevine is shown to contain at least three unsubstituted methyl groups by the



XIII



XIV



XV

Kuhn-Roth determination,[16] thus eliminating C_{21} and C_{27} as possible points of hydroxyl attachment. Furthermore, optically active N-methyl-β-pipecoline (XIV) may be isolated[18] upon hydrogenation of the mixture obtained by distillation of cevine from zinc dust and soda lime. C_{25} can thus be rejected as a possible point of attachment, since it is highly improbable that a hydroxyl group at this point could be replaced by hydrogen with maintenance of asymmetry under these strenuous conditions. C_{23} and C_{24} may also be rejected as possible sites for hydroxyl attachment since Jacobs and coworkers, in isolating a long series of relatively simple pyridine and piperidine bases from cevine, have never been able to detect the presence of 4-pyridones or phenolic 3-hydroxy pyridines, products which were easily isolated upon degradation of similar alkaloids containing oxygen in ring F.[19] Since all possible points of attachment have been eliminated, with the exception of C_{16}, C_{17} and C_{20}, the three hydroxyl groups may be assigned to these positions.[3] Further, more conclusive evidence has recently been obtained which verifies the attachement of hydroxyls at the above three positions in a positive fashion.[3,9,16,20] Thus, we may write the complete structure for cevine (XV), apart from the steric relationships.

The behavior of the alkamines from other ester alkaloids of Veratrum species parallels that of cevine very closely, especially with regard to the isomerization possible via the masked α-ketol system, and it has been

suggested that they differ only in the number, and possibly position, of the hydroxyl groups on the C-D-E-F system.[3]

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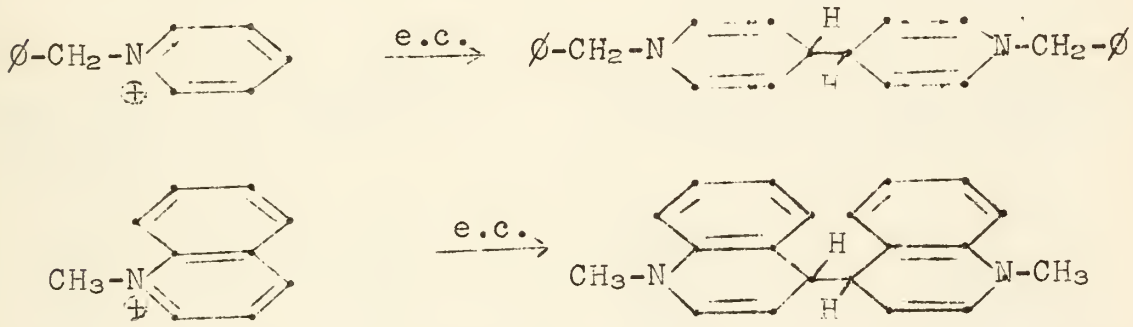
THE ELECTROLYTIC REDUCTIVE COUPLING OF HETEROCYCLIC NITROGEN COMPOUNDS

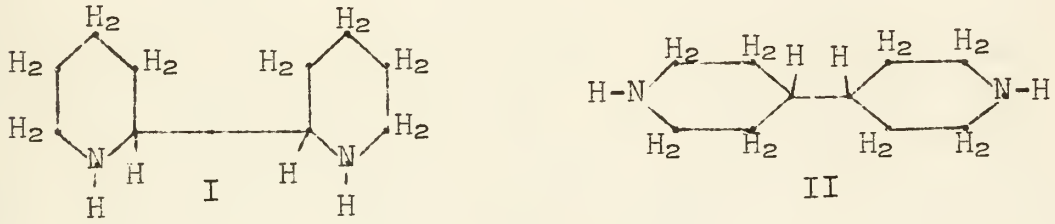
Reported by Richard A. Strehlow May 21, 1954

In 1896 Ahrens[1] reduced pyridine electrolytically to piperidine in a reported yield of 95%. Marie and Lejeune[2] (in 1925) and Cook and Rider[3] (in 1937) showed that the pyridine was not completely reduced. Marie and Lejeune reported a 65% yield of piperidine and about a 20% yield of a tetrahydropyridine.

Emmert, in 1909, subjected certain pyridinium and quinolinium salts to electrolysis and found that the principal products of the reductions were coupled products, as shown immediately below.



Emmert[5] later found that in the reduction of pyridine, both 1,1'-bipiperidine (I) and 3,3'-bipiperidine (II) were formed.



Rulke and Clotofski[6] reported bi- and poly-piperidines were formed from pyridine in presence of a low excess of sulphuric acid. Drosdov[7] stated that the formation of the coupled products was a function of the sulphuric acid concentration and not of temperature, current density, or pyridine concentration. Miller[8] studied the electrolytic reduction of petroleum nitrogen bases (pyridine and quinoline derivatives) in an attempt to obtain piperidine and tetrahydroquinoline compounds. Some of the results of this work are tabulated in Tables A, B and C.

TABLE A

N of acid	Reduced %(wt)	Coupled %(wt)	Unreduced %(wt)
1	33	26	7
2	43	21	11
3.3	65	small	18
4.5	66	nil	22
6	67	nil	22

TABLE B

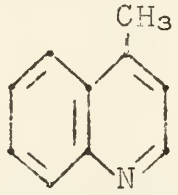
T °C	Reduced %	Coupled %
27	51	24
50	56	16
70	59	small

TABLE C

Starting material % (vol)	Reduced %	Coupled %	Time (hours)
14.8	65	Small	6
25	62	10	10
37.5	56	15.5	12
50	40	34	18

These data are consistant with the view that in order to couple, it is necessary for the pyridinium or quinolinium ions to deposit on the surface of the electrode. With an increase in hydrogen ion concentration, hydrogen is discharged to an increased extent. This increases the likelihood of an adsorbed pyridyl radical reacting with hydrogen rather than coupling. The data are also consistant with the findings of Szmaragd and Briner[9,10] who reported that pyridine, quinoline, and several of the hydroxyquinolines acted as depolarizers (i.e., they lowered the potential of hydrogen ion reduction).

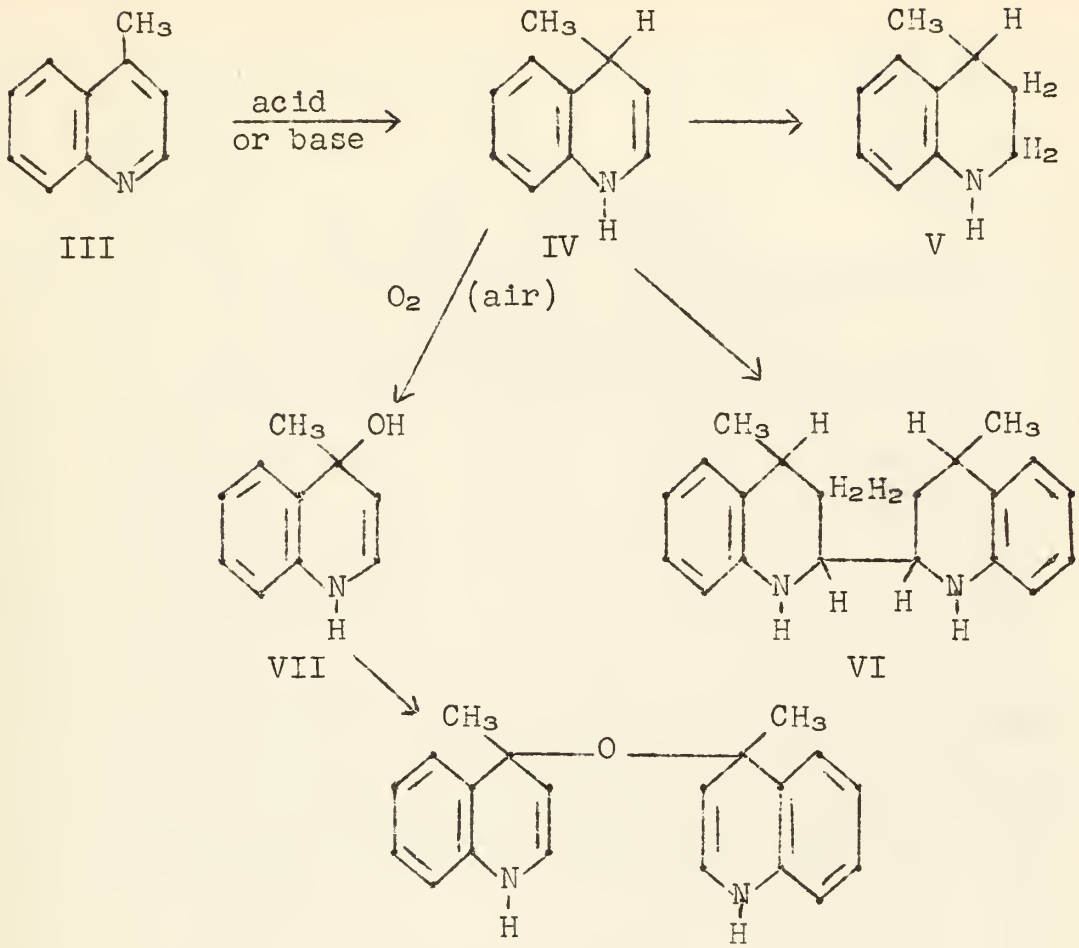
Levchenko and Zats[11,12] have reported on the electrolytic reduction of lepidine (III) in both acidic and basic media.



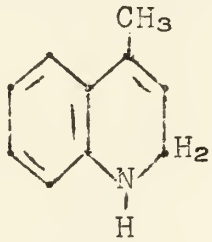
III

In acidic medium; dihydrolepidine (IV), tetrahydrolepidine (V), and dihydrolepidine dimer (VI) were obtained. In basic solution; tetrahydrolepidine (V), dihydrolepidine dimer (VI), and two other crystalline substances were found. These two compounds proved to be dihydrolepidine oxide (VIII) and 3-hydroxydihydrolepidine (VII). The reaction scheme

given by Levchenko and Zats is shown below.



The authors did not establish the fact that the dihydrolepidine obtained in acid medium was the 1,4 isomer rather than the 1,2-dihydrolepidine (IX), just as Marie and Lejeune[2] (vide supra) did not establish the structure of the tetrahydropyridine they obtained from pyridine.



IX

Chemical reduction by Zats and Levchenko yielded compounds V, VIII, and some VI[13], but no chemical reduction has yet been reported which would be as suitable for the preparation of compounds such as VI as the electrolytic method. In the pyridine series, however, both pyrolysis in presence of ferric chloride and reduction with metallic sodium have produced bi- and tri-pyridines.[14]

Little work has been done to elucidate the mechanism of the electrolytic reduction of these compounds.[15]

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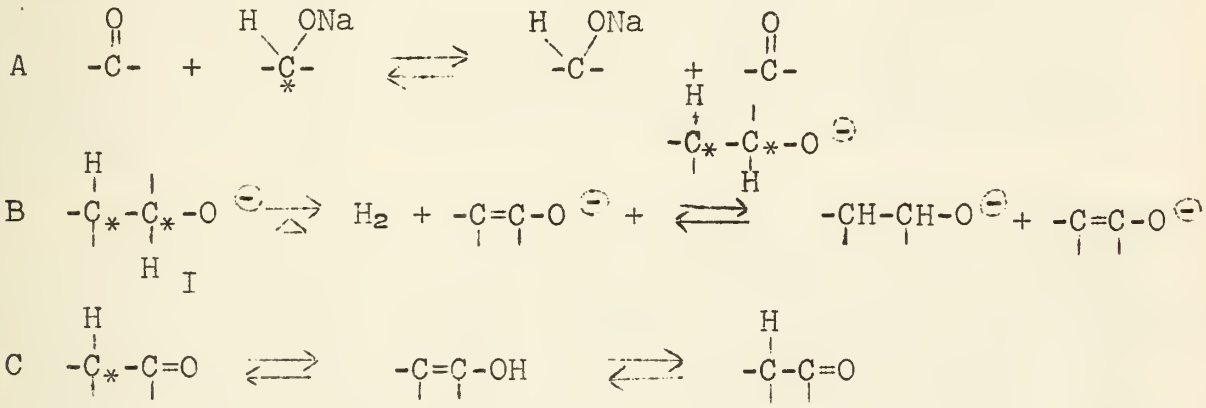
MECHANISM OF THE ALKOXIDE-CATALYZED CARBINOL-CARBONYL EQUILIBRIUM

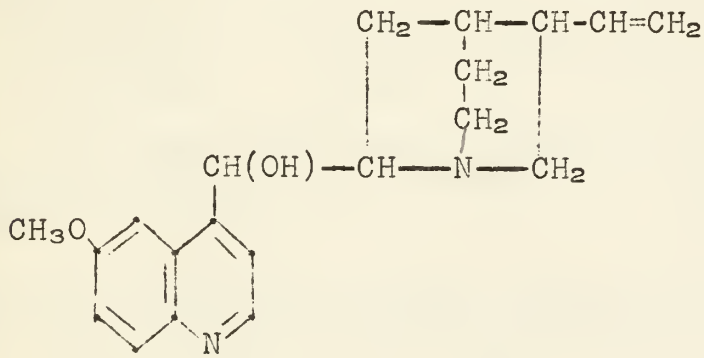
Reported by Richard W. Fulmer May 21, 1954

Many examples in the literature point to the fact that alcohols of general structure I may be brought to stereochemical equilibrium by treatment with alkoxide ion. Several schemes have been advanced to account for this. Rather early Wagner-Jauregg[1] and Hückel[2] suggested that the equilibration is initiated by direct dehydrogenation of a sodium alcoholate to yield an aldehyde or ketone which may then participate in a reversible Meerwein-Ponndorf-Verley reduction and Oppenauer oxidation. Wagner-Jauregg indicated only the general scheme A, while Hückel proposed the more detailed scheme B to accommodate equilibration.



Doering and coworkers[3,4] have suggested that the alkoxide catalyzed enolization of the ketones corresponding to the alcohols of type I would be sufficient to account for the stereochemical equilibration of the carbonyl compound, as represented by a combination of schemes A and C.

Since quinine has two asymmetric centers there are four possible products that would be obtained should the racemization go through an enol intermediate. Doering[4] has shown that all of these can be isolated from the reaction mixture. Unfortunately this system leads to an anomalous re-



sult concerning the carbonyl requirement in the system. He found that quinine may be converted to quininone in the absence of any ketone initiator; that is, quininone is formed at the expense of either one half or one equivalent of quinine which may go to dihydroquinine. This then allows the normal racemization of quinine under the usual oxidation-reduction

mechanism even in the absence of added carbonyl compounds.

Experimentally Doering and Aschner[3] have shown that the racemization of (-)-phenylmethylcarbinol by potassium t-butoxide at 100° can be completely inhibited by excluding oxygen, potassium peroxides, and carbonyl compounds, and that, under otherwise non-racemizing conditions, the addition of a rapid oxidation-reduction system (fluorenol-fluorenone) causes 56% racemization. Likewise, (-)-2-methylbutanol-1, stable to boiling for twenty hours with 5 mole % sodium, is racemized in a few hours by the addition of benzophenone.

The fact that a carbonyl compound is required in the equilibration can be interpreted further to indicate that a reversible oxidation-reduction process is the essential mechanism. No initiating carbonyl compound was formed in the above experimental work by the elimination of hydrogen gas as proposed by both Wagner-Jauregg and Hückel, at least not at the comparatively low temperatures used; however, at higher temperatures where alkoxide ion is known to lose hydrogen, dehydrogenation may serve as a means of introducing initiating carbonyl compound.

Mechanism B also places a specific structural requirement on the alcohol since it should be impossible stereochemically to equilibrate a secondary alcohol having no alpha hydrogen atom which could be removed directly to form the corresponding enolate ion. Both α- and β-fenchol can be epimerized when a rapid oxidation-reduction system (fluorenol-fluorenone) is added. Even non-enolizable ketones such as fluorenone and benzophenone are able to initiate stereochemical equilibration of the fenchols, though with fenchone as the carbonyl compound the rate is so slow as to require the addition of a different system to achieve the reversible oxidation-reduction and accompanying epimerization. In the very slowly reacting fenchol-fenchone system (1), the addition of a system that interacts rapidly (2), introduces a cross reaction (3) of undetermined rate that allows a more rapid establishment of the equilibrium (1).

$$\text{Fenchol}^* + \text{fenchone} \overset{1}{\rightleftharpoons} \text{fenchone} + \text{fenchol}$$

$$\text{Fluorenol} + \text{fluorenone} \overset{2}{\rightleftharpoons} \text{fluorenone} + \text{fluorenol}$$

$$\text{Fluorenone} + \text{fenchol}^* \overset{3}{\rightleftharpoons} \text{fluorenol} + \text{fenchone}$$

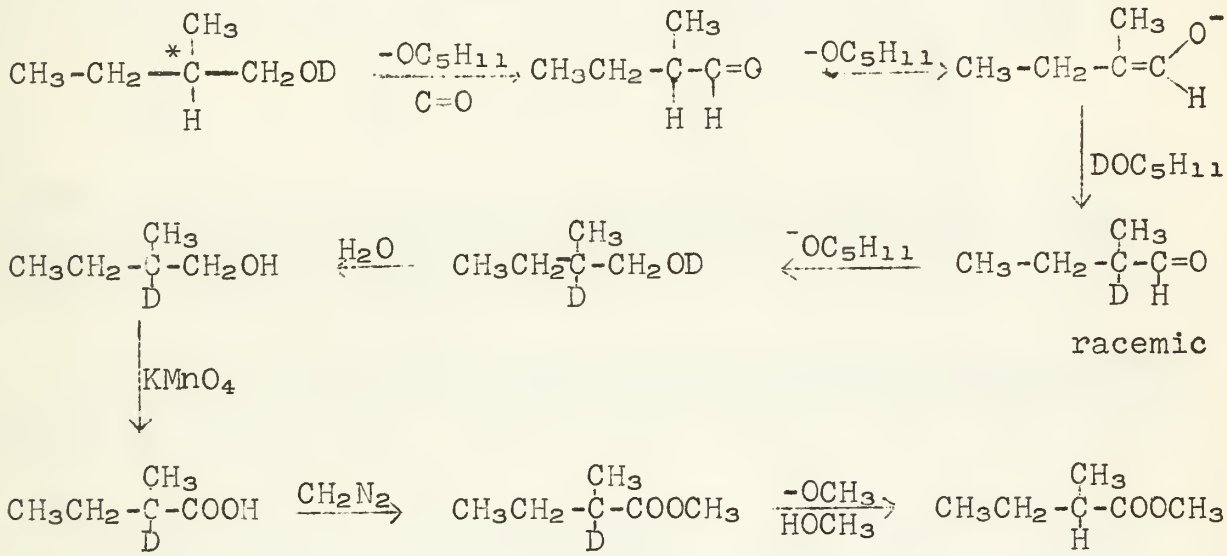
From these considerations Doering rejected scheme B as inoperative at least at the moderate temperatures of his experimental work.

In a more recent study of the specific mechanism of the reversible carbinol-carbonyl half cell, Doering and Aschner[5] have investigated two additional aspects in the racemization of (-)-2-methylbutanol-1: namely, the attempted interception of free radical intermediates, and the origin of the reducing hydrogen atom.

In addition to the active carbinol and a 5 mole % of sodium alkoxide, Doering and Aschner have variably added nothing, a carbonyl compound as oxidant, diphenylamine or

thiophenol as powerful free radical inhibitors, Bindschedler's Green [bis-(p-dimethylaminophenyl)-amine], benzhydrol, and pinacol. Their results again indicate that a carbonyl oxidant is necessary, for without it there was no reaction. Neither diphenylamine nor thiophenol showed any retarding effect on the racemization. Bindschedler's Green (equal quantities of the oxidized and reduced forms disproportionate in strong base to a free radical) failed to initiate the racemization in the absence of a carbonyl compound, and had no effect on the equilibration in the presence of benzophenone. Pinacol, which is known to fail in the usual Meerwein-Ponndorf-Verley reduction and Oppenauer oxidation reactions, failed to initiate the racemization. From all the data, Doering concluded that it was quite improbable that free radicals are involved in any step in the racemization of the active carbinol.

Doering and Aschner also studied the origin of the reducing hydrogen using racemization as a measure of the oxidation-reduction and solvent deuterium as a tracer for hydrogen. The following scheme outlines the experimental pathway used after first testing the validity of the individual steps.



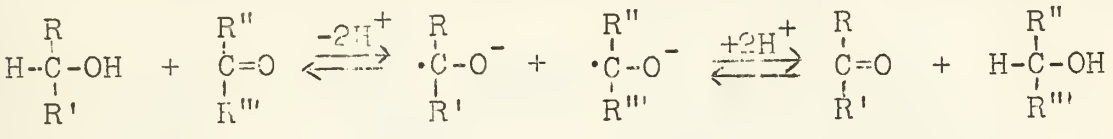
This sequence requires that any deuterium picked up from the labeled n-amyl alcohol used as solvent must become attached directly to the tertiary carbon. The retention of all deuterium in the permanaganate oxidation demonstrates that none was bonded directly to the carbinol carbon.

Similar experiments with aluminum alkoxide gave a lower percentage of deuterium on the asymmetric carbon indicating a 2.5 fold difference in the rate of reaction between hydrogen and deuterium. A reasonable explanation is that the rate determining step in the racemization catalyzed by aluminum alkoxide is the making or breaking of a carbon-hydrogen bond, therefore enolization; whereas in the sodium alkoxide catalyzed reaction, the oxidation-reduction may be rate determining.

The labeling experiments demonstrate that the solvent hydrogen does not become attached directly to the carbinol carbon but rather suggests that the hydrogen is transferred

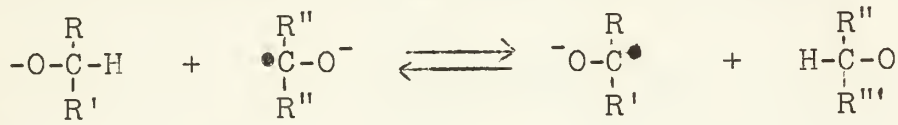
directly from carbinol carbon to carbonyl carbon.

The data thus far allowed elimination of several of the proposed mechanisms for the carbinol-carbonyl system. Michaelis and Schubert[6] in 1938 suggested for the system a mechanism similar to one he had established for the duroquinone-durohydroquinone and benzil-benzoin system. Based mainly on single electron steps and dismutation as represented in the scheme, it is in accord with the structural and reversibility conditions,



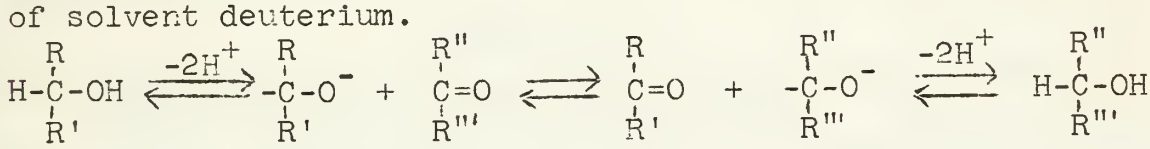
but violates the work of Doering on non-intervention of solvent deuterium and the apparent nonexistence of free radical intermediates. However, when structural features may greatly increase the stability of the hypothesized free radicals, the one electron steps can often be measured electrochemically. Thus in some cases the Michaelis mechanism may be more strongly supported.

A similar chain sequence may be suggested to account for the oxidation-reduction. In this system, however, there is

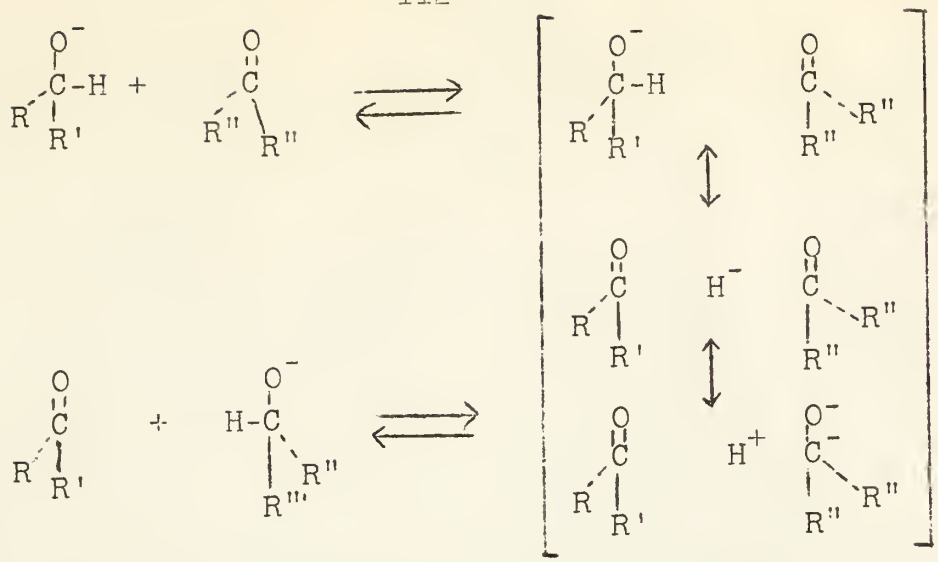


direct transfer of hydrogen from carbon to carbon, but it still appears inconsistent with Doering's free radical data. Also it does not entirely explain the effectiveness of aluminum alkoxide as catalyst.

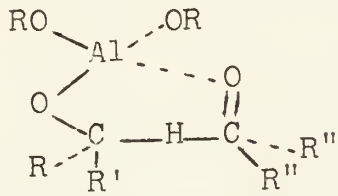
A system involving dianions would allow an ionic mechanism in which two electrons are transferred simultaneously but again the results were inconsistent with the non-intervention of solvent deuterium.



Woodward, Wendler, and Brutschy[7] have formulated a mechanism for the equilibrium involving the direct transfer of hydrogen with its two bonding electrons from one carbon to another. The alkoxide ion apparently is trying to expel an hydride ion by virtue of its negative charge and, as it approaches the electron deficient carbonyl carbon, there appears to be a resonance stabilized transition state. In this transition state there is a lower energy barrier for the transfer of hydrogen than would be the case if a free hydride ion were ejected and then rebonded to carbon. This mechanism is in accord with the various conditions of the reversible oxidation-reduction.



A mechanism of this type will also explain the observed effectiveness of aluminum alkoxide as a catalyst. The energy of the transition state is lowered by partial covalent bonding with the electron accepting character of the carbonyl group. The resonance structures for the transition state are similar to those above



The carbinol-carbonyl equilibrium apparently falls into a class of oxidation-reductions which have in common base-catalyzed, direct hydrogen transfer as the effective mechanism. Included are the Cannizzaro reaction, the intramolecular disproportionations of glyoxal and phenylglyoxal, and of course the intermolecular Meerwein-Ponndorf-Verley-Oppenauer interconversions.

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